

Infusion-Related Reactions Among Cancer Patients Receiving Immune Checkpoint Inhibitors: The ARON-MOUSEION-013 Systematic Review and Meta-Analysis

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Purpose: To investigate the incidence of Infusion-Related Reactions (IRRs) among cancer patients receiving Immune Checkpoint Inhibitors (ICIs) and immune-based combinations.

Patients and Methods: The ARON-MOUSEION-013 was registered in PROSPERO (CRD420251018433). Observational, randomized and quasi-experimental studies were included in the present review, and rates in IRR among cancer adults (≥ 18 years) receiving ICIs were recorded and then analyzed.

Results: A total of 4 records were considered for analyses, with a total of 55 observations and 35 events. The overall prevalence of IRR, considering Any Grade, was 67.4% [95% CI: 3.9%; 99.1%]. Considering Grade ≥ 3 , a total of 55 observations and 8 events were registered. The overall prevalence of irAEs in IRRs was 6% [95% CI: 0.2%; 74.7%].

Conclusion: Mild-to-moderate IRRs are not rare events in patients receiving ICIs. IRRs may be avoided to manage these infusions slowly; however, severe reactions require emergency handling.

Keywords: immunotherapy, infusion-related reactions, injection site reaction, neoplasms, cancer

Introduction

Unfavorable reactions to the infusion of biological or pharmacological substances are known as infusion-related reactions (IRRs), according to the National Cancer Institute (NCI).¹ IRRs may occur with several parenterally delivered anticancer therapies, ranging from cytotoxic chemotherapy to immune checkpoint inhibitors (ICIs), whether administered intravenously or subcutaneously.² IRRs occur on the day of or the day after infusion and commonly resolve 2 days after onset. The frequency of IRR varies widely,³⁻⁵ since numerous parameters impact on this, as autoimmune disorders, B cell malignancies, prophylaxis regimens with or without corticosteroids and subsequent infusions. The incidence of IRR decreases with subsequent infusions.³

These reactions are rarely severe (grade 3 or 4) and reported in 10% of patients,^{6,7} more present in B-cell malignancies than in autoimmune disorders.⁸ In a previous study collecting data from 2005 to 2015 on IRR frequency

in cancer patients, the steroid administrations prevent IRR.⁹ In autoimmune disorders, corticosteroid use in prophylaxis was strictly associated to a decrease in IRR rate.⁸ In autoimmune disorders, IRRs are lower, also due to the administration of corticosteroids.¹⁰ The frequency of severe IRR is less than 5% in appropriate premedication procedure, close monitoring and urgent management whenever it is needed.¹¹

The essential element, which is most recorded to be linked to IRR occurrence and severity, is the lymphocyte count.³ However, when assessing clinical stage, tumor burden is not linked to the occurrence of IRR,^{7,9} indicating that the concentration of targeted cells, rather than tumor progression, is an important element for the occurrence of IRR.¹²

IRR immune manifestations can theoretically develop from several processes, like: IgE mediated hypersensitivity or anaphylactic reaction, immunogenicity of ICI treatments, complement activation and cytokine-release syndrome (CRS).¹³ In all these cases, clinical manifestations are very similar. All these reactions can be tested by elevated serum level of tryptase.¹⁴ It was initially suggested that IRR was activated by the complement system activation which rapidly occurred after ICIs administrations, correlating cytokine secretion and the complement activation with the severity of IRR. Conversely, it was observed that higher frequency and severity of IRR reduced complement activation. Thus, complement activation may be not considered the main initiator in IRR.¹⁵

However, adverse events remained a concern requiring further investigations, since both the pathogenic process of IRR and its related mechanism remain unknown. IRR induces the secretion of cytokines, which interact with NK cells. Evidence supports that this interaction may cause the secretion of cytokines by both NK cells and B cells.¹⁶

To prevent a possible IRR, patients can receive premedication with diphenhydramine and acetaminophen. Treatment related IRR management is provided in the study protocol, and a careful evaluation has been requested to confirm or exclude other potential causes.¹⁷

Regarding cytotoxic agents, the most frequently linked to infusion responses drugs include procarbazine, bleomycin, taxanes, pegylated liposomal doxorubicin, asparaginase, and platinum salts.¹⁸ Risk factors for standard infusion reactions for cytotoxic agents include previous allergic reactions, asthma, female sex, higher drug doses, iodine and seafood allergies, preexisting cardiac or pulmonary dysfunction, previous exposure to the drug, concomitant β -adrenergic blocker therapy, and concurrent autoimmune disease.¹⁹

The symptoms related to IRRs typically present as low-grade fever, chills, headache, or nausea. High-grade reactions can include additional symptoms of tachycardia, changes in blood pressure, hypoxemia, chest pain, cough, shortness of breath, wheezing, flushing, sweating, urticaria or pruritis, angioedema, and presyncope or syncope.²⁰

Both immune-mediated and non-immune-mediated mechanisms may be involved in the development of IRRs, which are often categorized as non-allergic reactions or immune-mediated reactions (or true allergies) to foreign proteins.²¹ In the case of the IRRs-induced by ICIs, it is generally assumed that less than 5% of patients receiving immunotherapy present a severe reaction to the infusion, but this prevalence depends on several factors such as the drugs and its specific immune system targets.²² Immune responses can be innate, adaptive or both.¹ The innate response is the body's first line of defense: a rapid, nonspecific response that is triggered by the chemical properties of an antigen. The innate response involves macrophages, neutrophils, natural killer cells, dendritic cells, basophils, eosinophils, antimicrobial peptides and proteins. The IRRs mediated by innate immunity are present before the exposure of the foreign substance and are generally unaffected by repeated exposure. In contrast, in IRRs mediated by adaptive immunity, each successive exposure to the drug enhances the immune system's defensive response and increases its effects. The adaptive response involves T cells, B cells, antigen-presenting cells and antibodies.²³

In ICIS, the IRRs related symptomatology might largely differ in terms of severity, also differently affecting physiological systems, and widely differing from patient to patient and between therapeutic agents.²⁴ For example, in the case of the anti-PD-L1 antibody, like avelumab, the IRRs are predominantly grade 1–3 in severity and manifest as chills, pyrexia and flushing.^{25,26} Regarding the prevalence, in avelumab-induced IRRs, it has been reported to be approximately one-quarter of all patients.¹⁷ A peculiar case among ICIs is the antibody avelumab, a fully human IgG1 monoclonal antibody that targets programmed death-ligand 1 (PD-L1) and that retains an intact Fc region, resulting in the ability to induce antibody-dependent cell-mediated cytotoxicity.¹⁸ For nivolumab, a PD-1 immune checkpoint inhibitor antibody, the frequency of drug-related hypersensitivity/infusion reactions of any grade varies from 1.6%, including two grade 3 anaphylactic reactions and one grade 4 hypersensitivity, to 5.3%; for pembrolizumab (another

PD-1 immune checkpoint inhibitor antibody), the frequency reported in clinical trials was 2%.²⁷ In case of severe reaction to the antibody infusion, the drug infusion should be discontinued and appropriate medical treatment should be administered.

Consequently, IRRs can be frequent, appearing mostly at first infusion, and requiring a specific premedication consisting in antihistamine and acetaminophen prior to the first 4 infusions.²⁸

Because of previous inconsistencies and disparities in the terminology, grading, and reporting of the occurrence of IRRs, it has been challenging to determine the incidence of IRRs, and despite the paucity of research on the topic, what is known about it indicates that the occurrence of IRRs varies depending on the cancer type, anticancer therapies, and administration of anticancer therapies.^{22,29}

The recent years have seen the development and advent of novel combination strategies based on immunotherapy and ICI-based treatment has established itself as a mainstay in several hematological and solid tumors.^{30–37} While the advent of immune checkpoint inhibitors that work by blocking the PD-L1 protein such as pembrolizumab, nivolumab, atezolizumab, durvalumab, avelumab, as well as the emerging of combinations of ICIs with anticancer agents, have represented a key step forward, some challenges remain, including the onset of toxicities, commonly defined as immune-related adverse events (irAEs).^{38–40} Among adverse events related to ICIs, evidence regarding the onset of IRRs is sparse in this setting.⁴⁰

Herein, the ARON-MOUSEION-013 systematic review and meta-analysis aimed to investigate the incidence of IRRs among cancer patients receiving ICIs and immune-based combinations.

Materials and Methods

Research Procedure

The MOUSEION-013 was registered in PROSPERO (CRD420251018433) and carried out with the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) (Figure 1).⁴¹ The PRISMA 2020 flow diagram templates are distributed in accordance with the terms of the Creative Commons Attribution (CC BY 4.0) license, which permits others to distribute, remix, adapt and build upon this work, for commercial use, provided the original work is properly cited. To view a copy of this license, visit <https://creativecommons.org/licenses/by/4.0/>

MeSH terms adopted as keywords were “Immunotherapy”, “Injection Site Reaction” and “Neoplasms” and research was performed throughout Embase, PubMed, Scopus and Web of Science databases without any time limits (Supplementary File 1).

Research question was recognized using the PIO approach (Supplementary File 2).

Inclusion and Exclusion Criteria

Only records published in English language and available in their full text versions were included. Moreover, observational, randomized and quasi-experimental studies were included in the present review. Rates in IRR symptomatology among cancer adults (≥ 18 years) receiving immune checkpoint inhibitor treatments were recorded and then analyzed.

The Selection Process

Identified records were registered in a systematic database search and uploaded to reference management software and then duplicates were excluded. Two independent reviewers (E.V. and L.M.) assessed their titles and abstracts to further include or exclude other selected records. Only the included articles were uploaded, and their full text versions were deeply evaluated for their eligibility. Disagreements on the selection process were discussed and, if the disagreement persisted, a new combined evaluation was performed, included a third reviewer in the discussion (A.R.).

Data was collected considering author(s), year of publication, sample size, and proportion of IRRs as adverse effects among cancer patients treated with immunotherapy.

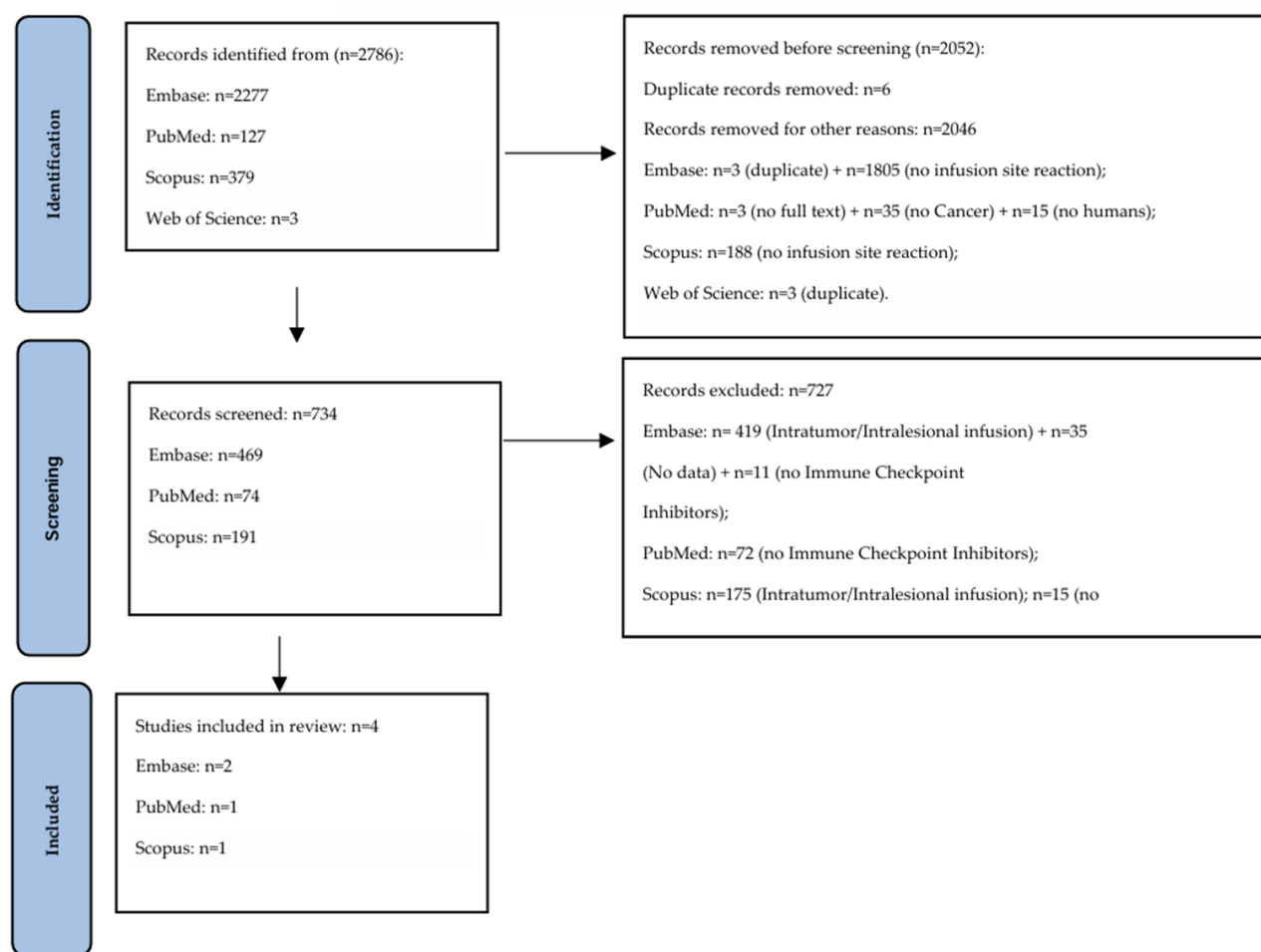


Figure 1 The PRISMA flowchart for records procedure.

Risk of Bias (Quality) Assessment

In observational studies, the presence of Risk of Bias was investigated using the risk of bias of exposures (ROBINS-E) tool.⁴² The tool consisted of seven sub dimensions exploring the presence of bias in the obtained results. These sub dimensions were recognized a shown in Figure 2.

Strategy for Data Synthesis

Studies were assessed for quality, and their related information was highlighted in a narrative approach thanks to Table 1. Statistical analysis was performed using the R environment (version 4.4.2) and the significance level of the analysis was set at $P < 0.05$.

The primary outcome of this meta-analysis was the proportion of subjects for whom the adverse event occurred (defined as the number of patients with at least one infusion site reactions event (irAE) divided by the total number of patients). To this research, a meta-analysis for proportions aimed at investigating the proportion of subjects for whom infusion site reactions events occurred among patients undergoing immunotherapy.⁴⁷

The effect size for each study was assessed using a logit transformation of the proportion of subjects for whom IRRs after immunotherapy infusions.⁴⁸

A generalized linear mixed model (GLMM) with a logit link function was employed to estimate the pooled effect, allowing for both within-study variability and between-study heterogeneity to be explicitly modeled.⁴⁹ A random-effects model was specified using the Hartung-Knapp adjustment to obtain more conservative and robust confidence intervals for

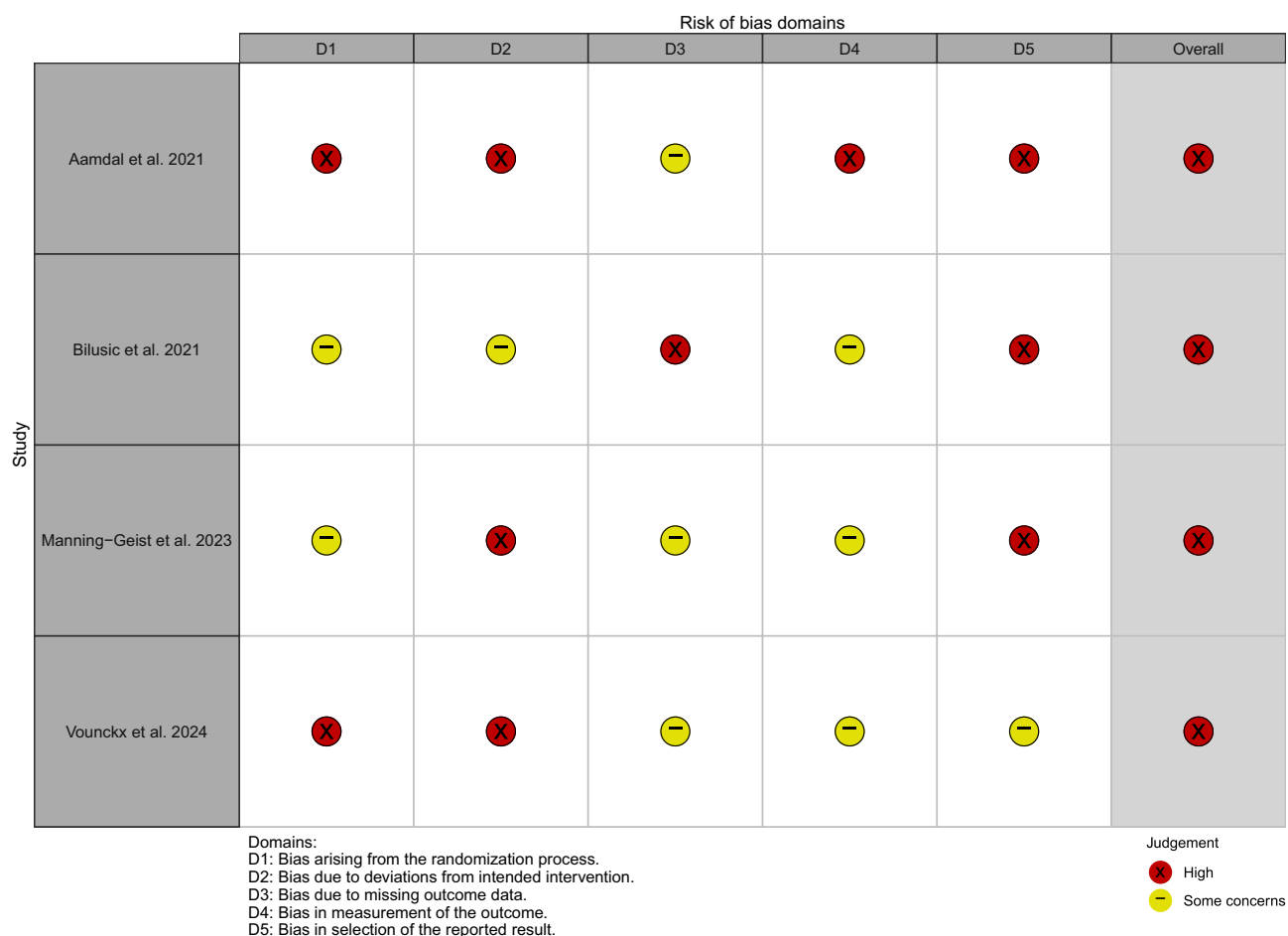


Figure 2 Risk of Bias assessment (Original).

the pooled estimates. Proportions were calculated for any grade of irAE and for grade ≥ 3 and two separate subgroup meta-analyses were performed, specifically one for any grade and one for grade ≥ 3 , respectively.

Heterogeneity among studies was assessed using χ^2 -based Q test. A significant Q value ($P < 0.05$) suggested the presence of significant heterogeneity between included studies. Additionally, the I-squared inconsistency index (I^2) was used to assess the percentage of true variability in the observed effects.^{50,51} I^2 statistics were adopted with 25%, 50%, and 75% indicating low, moderate, and high heterogeneity degrees, respectively. Because we expected a high degree of heterogeneity among studies, a random-effects pooling models were implemented.⁵¹

Forest Plots was generated to report the results of the meta-analysis. Publication bias was not formally assessed, as the number of included studies ($n = 4$) was below the recommended threshold for reliable evaluation using funnel plot-based methods or Egger's test.⁵²

Results

Selected Studies

A total of 2786 records were identified from Embase ($n = 2277$), PubMed ($n = 127$), Scopus ($n = 379$) and Web of Science ($n = 3$) databases. Of those, 2052 records were excluded as 6 were duplicates and 2046 did not deal with IRRs or not cancer diseases. Thus, 734 were further read in their abstracts, and 727 were additionally removed since they did not focus on IRRs symptoms. Finally, 4 records were considered for analysis^{43–46} referring to Embase ($n = 2$), PubMed ($n = 1$) and Scopus ($n = 1$) databases (Figure 1). All features of the included studies were displayed in Table 1 included the main IRRs symptomatology differentiated between “any grade” and “grade 3 or 4”.

Table 1 Characteristics of the Selected Studies (n = 4)

Author(s) Publication Year	Study Design	Cancer Typology	Immunotherapy Treatment	Total Patients No.	Gender Female Male	Age	IRRS Incidence in Immunotherapy Treatment	
							Any Grade	Grade 3 or 4
Aamdal et al 2021 ⁴³	Phase I/ II	Metastatic Melanoma	Ipilimumab	n = 9	Female: n = 5 Male: n = 7	57 (44–74) years	n = 4	n = 1
Bilusic et al 2021 ⁴⁴	Phase I	Metastatic Castration – Resistant Prostate Cancer	Recombinant yeast-CEA vaccine (GI-6207)	n = 22	Female: n = 15 Male: n = 10	52 (39–81) years	n = 22	n = 7
Manning-Geist et al 2023 ⁴⁵	Phase I	Ovarian Cancer	Nivolumab	n = 11	–	62 (40–74)	n = 7	n = 0
Vounckx et al 2024 ⁴⁶	Phase II	Solid Tumors	Avelumab/Ipilimumab	n = 13 Arm A n = 10 Arm B n = 3	Arm A Female: n = 3 Male: n = 7 Arm B Female: n = 1 Male: n = 2	Arm A 61.5 (35–73) Arm B 55 (35–65)	n = 2	n = 0

Any Grade

A total of 4 studies were included for these analyses, with a total of 55 observations and 35 events.^{35–38} A moderate heterogeneity was present among the studies ($P < 0.001$; $\tau^2 = 5.03$; $I^2 = 42.7\%$ with a 95% C.I.: [0%; 80.8%]). The result of the meta-analysis shown in the Forest Plot (Figure 3) displayed the overall prevalence of adverse event infusion site reactions, considering Any Grade, was 67.4% (95% CI: [3.9%; 99.1%]). Both the symmetry of the Funnel Plot (Figure 4) and the Eggers' test ($\beta = 3.88$; 95% CI = [−3.91; 11.67]; $P = 0.432$) indicate that no publication bias was present. The limited number of studies included could reduce the statistical power to identify such bias.

Grade ≥ 3

Four studies were considered for this analysis, with a total of 55 observations and 8 events. The heterogeneity between the studies was not significant ($P = 0.729$; $\tau^2 = 2.13$; $I^2 = 0\%$; 95% CI: [0%; 84.7%]). The Forest Plot (Figure 5) reported the overall prevalence of irAEs in IRRs considering Grade ≥ 3 was 6.2% [95% CI: 0.2%; 74.7%]. Both the Funnel Plot (Figure 6) and the Eggers' test ($\beta = -2.42$; 95% CI: [−2.67; −2.18; $P = 0.003$) indicated the presence of publication bias. Likewise, the small sample of studies may have reduced the power to detect bias.

Discussion

The MOUSEION-013 systematic review and meta-analysis explored the rate of IRRs among cancer patients receiving ICIs and immune-based combinations.

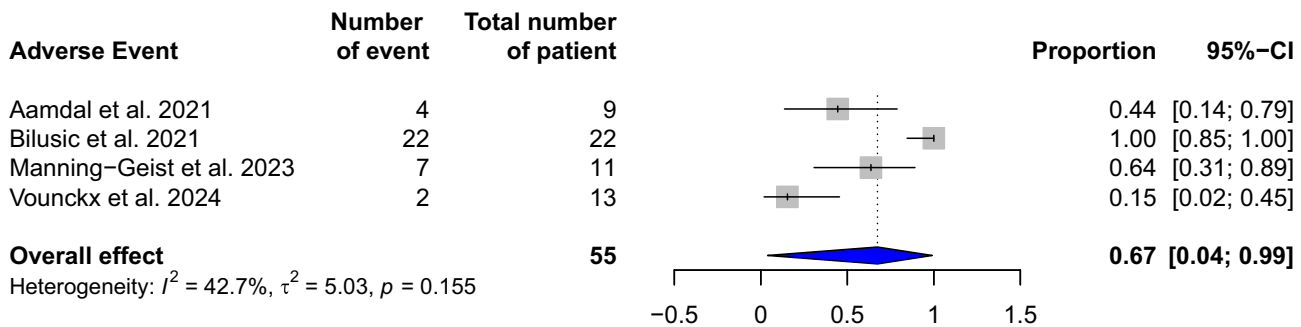


Figure 3 Forest Plot in proportion for Any Grade.

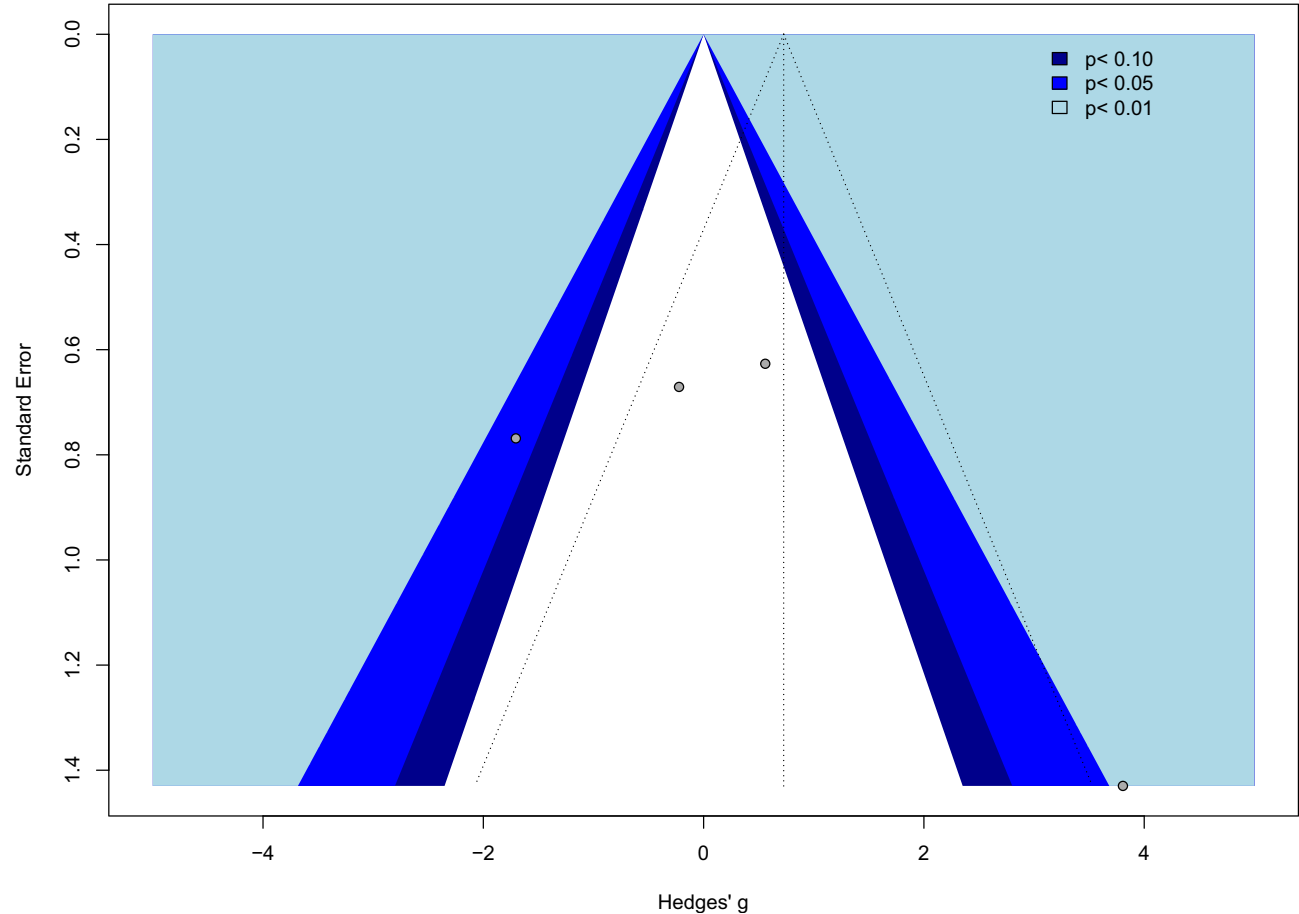


Figure 4 Contour-enhanced Funnel Plot for Any Grade.

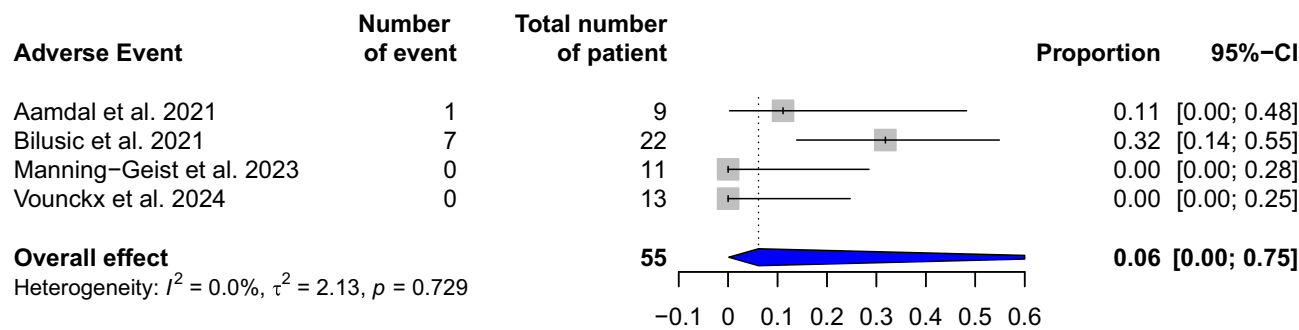


Figure 5 Forest Plot in proportion for Grade ≥ 3 .

Nowadays, combination therapy with ICIs for cancer is increasing. IRRs represent an issue for cancer patients also implicating intensive challenges in oncology practices.^{53–56}

Most cancer treatments, covering both cytotoxic agents and biologics, could raise risk for infusion reactions and their related symptomatology could vary from mild to moderate intensity, such as flushing to life-threatening events.⁵⁷ During the infusion of ICIs, several irAEs have just been associated to different severe hypersensitivity reactions, like a complex of chills, fever, nausea, asthenia, headache, skin rash and pruritus.^{58–60} However, etiologies in ICIs infusion reactions continued to be ambiguous. ICIs interplayed with their molecular factors in blood and tumor cells, promoting the secretion of inflammatory cytokines, being involved in a wide range of symptoms linked with infusion reactions,⁶¹ as

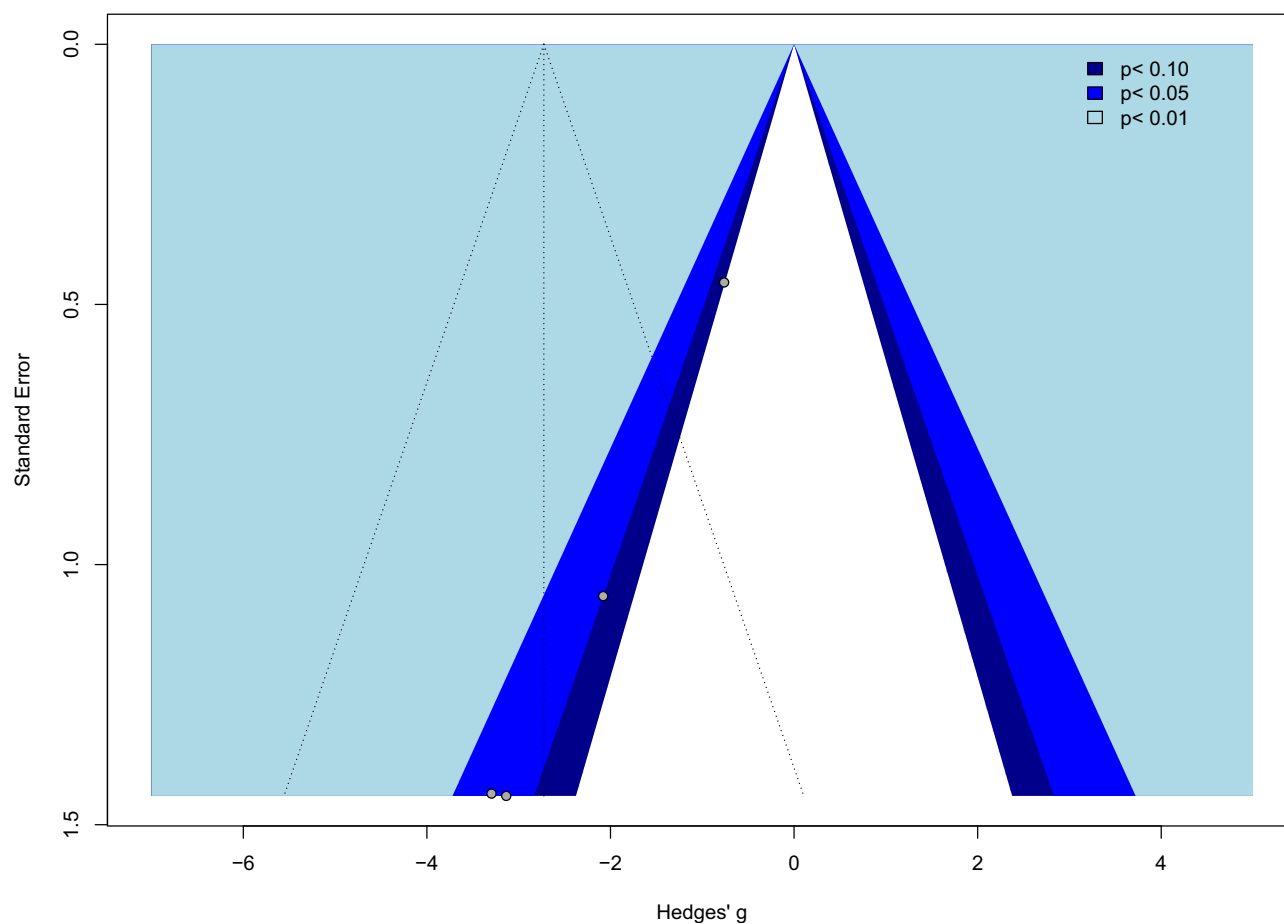


Figure 6 Contour-enhanced Funnel Plot for Grade ≥ 3 .

fever, chills, nausea, vomiting, hypotension, and dyspnea.⁶² Thus, we conducted a meta-analysis to systematically investigate the incidence rate of IRRs among cancer patients treated with ICIs, since we did not find any RCTs to compare the incidence in ICIs that in chemotherapy or placebo counterparts.

Our 55 observations and 35 events reported 67.4% (95% CI: [3.9%; 99.1%]) prevalence in irAEs of IRRs in Any Grade with no publication bias (Figures 3 and 4). On the other hand, considering Grade ≥ 3 , the prevalence registered was 6% (95% CI: [0%; 38.7%]) with also the presence of publication bias (Figures 4 and 5). This potential bias should be interpreted with caution, as Egger's test is known to have limited statistical power when applied to meta-analyses with a small number of studies, which is the case for this subgroup. The apparent asymmetry could also reflect true heterogeneity in study design, patient populations, or reporting standards rather than systematic bias. Nevertheless, the presence of bias cannot be excluded and underscores the need for more high-quality studies reporting severe IRRs to strengthen the robustness of future meta-analyses. Anyway, also in phases III and IV, IRRs incidence is quite low, as reported in the [Supplementary File 3](#). However, literature explained that ICIs combinations and their related irAEs varied from cancer typologies and therapeutic protocols.^{63–65} Thus, some studies have begun to deeply investigate the irAEs caused by added toxicities and the clinical value associated.^{66,67}

A recent meta-analysis focused on IRRs in patients with genitourinary tumors treated with ICIs, including 10,001 patients from 12 RCTs showed that the combination of ICIs to other therapies resulted in higher rates of grade 1–5 IRRs but not grade 3–5. In the subgroup of patients with RCC, the combination of ICI plus tyrosine kinase inhibitor (TKI) compared to sunitinib did not increase the risk of IRRs.⁶⁸ The increasingly widespread use of ICIs in oncology and other medical disciplines must ensure patient safety and optimal outcomes, requiring careful monitoring at the start of infusion, rapid recognition and appropriate clinical assessment of IRRs and their severity, followed by prompt treatment. The lack

of standardization in the prevention, management, and reporting of IRRs in cancer treating institutions represents not only a quality and safety gap but also a disparity in care.

Since IRRs have been reported as a frequent adverse effect in ICIs, training and communication among an expert and/or specialist and also oncology nurses should be considered as a key element to achieve a successful management of those patients^{69,70} to better manage them in these irAEs. Additionally, patient education seemed to be essential to also provide patient-specific educational materials to early identify signs or symptoms of an irAE.⁷¹ In this way, a prompt IRR management could avoid fatal conditions,^{72,73} with inevitably infusion rate reductions until interruptions according to the grade of severity.⁷⁴

The ARON-MOUSEION-013 systematic review and meta-analysis had some strengths and limitations to be acknowledged. Among the strengths of the current analysis, the study included several different clinical trials by using the most updated data in terms of safety and adverse events, and belonged to the international MOUSEION projects, that has seen the publication of several papers and studies exploring irAEs in cancer patients receiving immunotherapeutic agents. However, some limitations should be underlined. First, the current meta-analysis was based on pooled data, and thus, the presence of confounding factors and single-patient variables (eg, patient age, comorbidities, concomitant medications, etc.) was not included. Second, all trials included patients treated with heterogeneous systemic treatments; all these agents present different and not superimposable efficacy and safety profiles, and thus, this element could have produced some bias affecting our results. Thus, the presence of selection bias cannot be excluded. However, the small number of available studies limited the statistical power of the meta-analysis and results in wide confidence intervals reducing the precision of the pooled estimates. Therefore, the present results should be interpreted with more caution. On the other hand, the present study represented a quantitative summary of the existing evidence and could serve as a reference point for the incidence of IRRs in cancer patients receiving immunotherapy.

Conclusions

ICIs and their related combinations have modified the scenario of cancer treatments.

Both physicians and nurses should pay attention to the safety profile to reach the optimal management of these patients with the highest clinical benefit.⁷¹ Mild-to-moderate IRRs were reported in the current literature for ICIs. Thus, IRRs may be avoided to manage these infusions slowly; however, severe reactions require emergency handling.^{75,76} However, future larger prospective studies will be necessary to better recognize IRRs incidence in ICIs administration, also to better organize ongoing training in this important issue including the care team to ensure that serious IRRs are avoided and promptly identified also including patient education, awareness, early detection and involvement.⁷⁷

Author Contributions

Conceptualization, E.V., A.R., F.S.M.M., A.S. and V.L.; methodology, E.V. and L.M.; software, L.M.; validation, A. R. and L.M.; formal analysis, L.M.; investigation, E.V., A.R., L.M.; data curation, E.V., A.R., L.M.; writing—original draft preparation, E.V.; writing—review and editing, E.V., V.M., O.C.; visualization, O.C., E.V., A.R., F.M., M.S.; supervision, E.V., A.R., O.B., A.S., F.S.M.M. All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

Dr Andrey Soares reports personal fees from Janssen, Pfizer, Bayer, Merck Serono, Novartis, Astra Zeneca and Adium, outside the submitted work. The authors report no other conflicts of interest in this work.

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