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Patterns of immune-related adverse events in patients treated with immune checkpoint inhibitors: a Brazilian real-world analysis

Padrões de eventos adversos relacionados ao sistema imunológico em pacientes tratados com inibidores de checkpoint imunológico: uma análise do mundo real brasileiro

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ABSTRACT

Objectives: To report real-world data of a cohort of patients treated with immune-checkpoint inhibitors in Brazil, with focus in immune-related adverse events. **Material and Methods:** In this retrospective study, we analyzed a cohort of patients with metastatic solid tumors treated at an oncology reference center with at least one dose of immune-checkpoint inhibitors (given as monotherapy or in combination with other agents). The safety profile was characterized through the incidence of adverse events, management and hospitalization. **Results:** We included 185 patients. Immune-related adverse events were observed in 92 of the 185 study patients (49.7%), including 16 patients (8.6%) with such events of grade 3 or 4, and 28 patients (15.1%) requiring systemic corticosteroid therapy. Thyroid disorders (20%), rash (17.8%), pruritus (11.4%) and colitis (11.4%) were the most frequent immune-related adverse events. Five (2.7%) patients discontinued immune-checkpoint inhibitors and 15 (7.0%) were hospitalized due to immune-related adverse events. Development of immune-related adverse events and immune-checkpoint inhibitors used in the first-line setting were associated with prolonged progression-free survival and overall survival in the multivariate analysis. Moreover, age <75 years old and ECOG score 0 or 1 were positively associated with overall survival in the multivariate analysis. **Conclusion:** This study based upon a Brazilian "real-world" data confirms the toxicity profile of immune-checkpoint inhibitors seen in clinical trials. In accordance with previous retrospective analyses, development of immune-related adverse events was associated with survival outcome of immune-checkpoint inhibitors treatment in patients with metastatic solid cancers.

Keywords: Brazil; Immunotherapy; Immune checkpoint inhibitors; Toxicity.

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RESUMO

Objetivos: Relatar dados do mundo real de uma coorte de pacientes tratados com inibidores de checkpoint imunológico no Brasil, com foco em eventos adversos relacionados ao sistema imunológico. **Material e Métodos:** Neste estudo retrospectivo, analisamos uma coorte de pacientes com tumores sólidos metastáticos tratados em um centro de referência em oncologia com pelo menos uma dose de inibidores de checkpoint imunológico (administrados em monoterapia ou em combinação com outros agentes). O perfil de segurança foi caracterizado pela incidência de eventos adversos, manejo e hospitalização. **Resultados:** Incluímos 185 pacientes. Eventos adversos relacionados ao sistema imunológico foram observados em 92 dos 185 pacientes do estudo (49,7%), incluindo 16 pacientes (8,6%) com tais eventos de grau 3 ou 4, e 28 pacientes (15,1%) necessitando de terapia com corticosteroides sistêmicos. Distúrbios da tireoide (20%), erupção cutânea (17,8%), prurido (11,4%) e colite (11,4%) foram os eventos adversos relacionados ao sistema imunológico mais frequentes. Cinco (2,7%) pacientes descontinuaram os inibidores de checkpoint imunológico e 15 (7,0%) foram hospitalizados devido a eventos adversos relacionados ao sistema imunológico. O desenvolvimento de eventos adversos relacionados ao sistema imunológico e inibidores de checkpoint imunológico usados no cenário de primeira linha foram associados a sobrevida livre de progressão prolongada e sobrevida global na análise multivariada. Além disso, idade <75 anos e pontuação ECOG 0 ou 1 foram positivamente associadas à sobrevida global na análise multivariada. **Conclusão:** Este estudo baseado em dados brasileiros do "mundo real" confirma o perfil de toxicidade dos inibidores do checkpoint imunológico observado em ensaios clínicos. De acordo com análises retrospectivas anteriores, o desenvolvimento de eventos adversos relacionados ao sistema imunológico foi associado ao resultado de sobrevida do tratamento com inibidores de checkpoint imunológico em pacientes com cânceres sólidos metastáticos.

Descritores: Brasil; Imunoterapia; Inibidores do checkpoint imunológico; Toxicidade.

INTRODUCTION

Immune checkpoint inhibitors (ICIs), such as anti-cytotoxic T-lymphocyte antigen-4 and anti-programmed cell death 1 (anti-PD-1) and its ligand, have revolutionized the treatment of several malignant neoplasms.[1,2] Initially, these drugs were approved as single agents; however, their use in combination with distinct ICIs, targeted agents, and chemotherapy has emerged as a successful strategy.[3]

Given the importance of checkpoint molecules in the modulation of the immune response, the clinical use of ICIs has resulted in a new toxicity profile, the so-called immune-related adverse events (irAEs).[4] Such events are mediated by the hyperactivation of the immune system, leading to autoimmunity-like reactions.[5,6]

Data generated during clinical trials cannot necessarily be generalized to real- world situations, especially because the study population is often underrepresented by particular subgroups, such as elderly people, those with borderline functionality (ECOG- PS≥2), or with brain metastasis, owing to the study's strict inclusion criteria.[2,7,8]

Therefore, this study aimed to describe the occurrence of irAEs among unselected patients with advanced solid tumors treated with ICIs in two Brazilian cancer centers and their association with clinical characteristics and disease outcomes.

MATERIAL AND METHODS

Patients

Participants included in this analysis were adults aged ≥18 years, with metastatic solid tumors, undergoing any line of treatment, who received at least one dose of ICIs as a single agent or in combination with other ICIs, chemotherapy, or targeted therapy between June 2015 and February 2021. We considered the first treatment with ICI for patients who received more than one line of immunotherapy. We excluded patients with an Eastern Cooperative Oncology Group (ECOG) performance status ≥3 and those who were administered ICIs in the context of a clinical trial. This study was approved by the Institutional Review Board of the Hospital Sirio-Libanês (HSL). The need for written informed consent from the participants was waived because of the retrospective nature of the study.

Data collection

Data collection was performed retrospectively based on the electronic medical records from an oncology reference center (HSL). Data collection included the following patient characteristics: age at treatment initiation, sex, ECOG performance status, body mass index (BMI), and smoking habits (active smoker, never smoker, or former smoker). Disease characteristics included the tumor type and site(s) of metastasis at the initiation of treatment. Treatment characteristics included treatment line, type of therapy, toxicities (both immune-related and non-immune-related), toxicity management, overall hospitalization, reason for treatment interruption, date of progression, and date of death. Steroid use was defined as >10mg of oral prednisone or its equivalent per day (supraphysiological dose). All irAEs were defined as events occurring during or after treatment, including diarrhea, colitis, pneumonitis, rash, endocrine dysfunction, hepatitis, and other adverse events considered at least possibly immune-related by the treating physician. Toxicity was assessed according to the Common Terminology Criteria for Adverse Events 5.0. The database follow-up ended in February 2021.

Statistical analysis

Patient, tumor, and treatment characteristics were described using summarized descriptive statistics, summarizing medians and ranges for continuous variables and frequencies, quartiles, and percentages for categorical variables. Efficacy data included overall survival (OS) and progression-free survival (PFS) and were estimated using the Kaplan-Meier method. PFS was defined as the time from the start of ICI treatment until disease progression or death from any cause, whichever occurred first. OS was defined as the time from the start of immunotherapy to death from any cause. Kaplan-Meier analysis was used to estimate the medians. A multivariable Cox proportional hazards model was used to estimate hazard ratios and 95% confidence intervals for the evaluation of prognostic factors and their association with both OS and PFS. A *p*-value<.05 was considered significant. Analyses were performed using the IBM SPSS statistics software (version 24.0, SPSS, Chicago, IL, USA) and R version 3.6.0 with R packages survival and forest model.

RESULTS

Patients and treatment baseline characteristics

A total of 185 patients were eligible for analysis and were included in this study. The median age was 67.3 years (range, 30.1-90.4) and 48 patients (25.9%) were ≥75 years old. Most patients were male (62.2%), current or former smokers (50.3%), and had an ECOG of zero or one (75.0%). The most common tumor histology was non-small cell lung cancer (NSCLC) (40.0%) and melanoma (10.8%). Brain metastases were reported in 18.9% of the patients. A total of 108 patients (58.4%) received ICI monotherapy, 22 (11.9%) received a combination of ipilimumab and nivolumab, and 55 (29.7%) received anti-PD-1 (L1) in combination with chemotherapy or a targeted agent. ICIs were administered as first-line therapy in 40% of the cases. The baseline patient characteristics are summarized in Table 1.

Table 1. Patients and treatment characteristics.

Characteristics	N=185 (100%)
Male gender	115 (62%)
Age, years	
Median (range)	67.3 (30.1-90.4)
ECOG performance status	
0	70 (37.8%)
1	69 (37.2%)
2	18 (9.7%)
NA	28 (15.1%)
BMI<18.5	9 (4.9%)
18.5-24.9	72 (38.9%)
25-29.9	68 (36.7%)
≥ 30	36 (19.5%)
Current or former smokers	93 (50.2%)
Number of previous treatments	
0	74 (40%)
≥ 1	111 (60%)
Cancer types	
NSCLC	74 (40%)
Melanoma	20 (10.8%)
RCC	12 (6.5%)
Urothelial carcinoma	11 (5.9%)
Other*	68 (36.7%)
Immunotherapy	
Monotherapy	108 (58.4%)
Immunotherapy + CT or therapy targeted	55 (29.7%)
Immuno-combined (ipi+nivo)	22 (11.9%)
BM	35 (18.9%)
On-label	161 (87%)

Legend: NA: Not available; BMI: Body mass index; NSCLC: Non-small cell lung cancer; RCC: Renal cell carcinoma; CT: Chemotherapy; Ipi: Ipilimumab; Nivo: Nivolumab; Imuno: Immunotherapy; BM: Brain metastasis; *Small cell lung cancer, head and neck squamous cell carcinoma, esophageal adenocarcinoma, esophageal squamous cell carcinoma, stomach adenocarcinoma, stomach carcinoma hepatocellular carcinoma, Merkel cell carcinoma, triple negative breast cancer, ovarian serous carcinoma, skin squamous cell carcinoma, mesothelioma, prostate adenocarcinoma, colorectal carcinoma, dermatofibrosarcoma, colon adenocarcinoma, cervical carcinoma, endometrioid carcinoma, uterine serous carcinoma.

Characteristics of immune-related adverse events

The median follow-up period after the first dose of ICI was 12.4 months (range, 0.03-77.4). A total of 125 patients (69.2%) had toxicity of any grade, while grade 3-4 events were reported in 12.4% of patients. No cases of grade 5 toxicity were reported. The most frequent toxicities were fatigue (32.9%), thyroid disorders (19.5%), rash (17.8%), nausea (12.9%), pruritus (11.4%), and colitis/diarrhea (11.4%).

Immune-related adverse events (irAEs) of any grade were reported in 49.7% of the patients. Skin reactions were the most frequent irAEs (n=45/185, 24.3%), followed by thyroid abnormalities (n=37/185, 20%) and colitis/diarrhea (n=21/185, 11.4%) (Table 2). Grade 3-4 irAEs were observed in 8.6% of patients. Twenty-eight patients (15.1%) received supraphysiological dose of steroid therapy. One patient required infliximab and vedolizumab for colitis grade 4 management, and another received rituximab for myositis grade 3 management. The permanent discontinuation and hospitalization rates due to irAEs were 2.7% and 7.0%, respectively. The irAEs that led to permanent discontinuation of therapy were colitis (n=2), arthritis (n=1), pneumonitis (n=1), and myositis (n=1).

Survival outcomes

Overall, the median PFS and OS were 8.3 months [95% confidence interval (CI), 6.7-11.9] and 29.6 months (95% CI, 21.4-38.8), respectively (Figures 1 and 2). The PFS rate at 24 weeks was 51.3% and the OS rate at 12 months was 54.6%. At the time of the data analysis cutoff, 32 patients (17.3%) were still receiving ICI treatment. The most common reason for treatment discontinuation was disease progression or death (109, 58.9%), followed by physician choice (19/185, 10.2%). Of the 19 patients who discontinued treatment without progression, 14 remained in follow-up. Only five patients stopped therapy due to toxicity (2.7%). For twenty (10.8%) patients, the reason for ICI discontinuation was not reported.

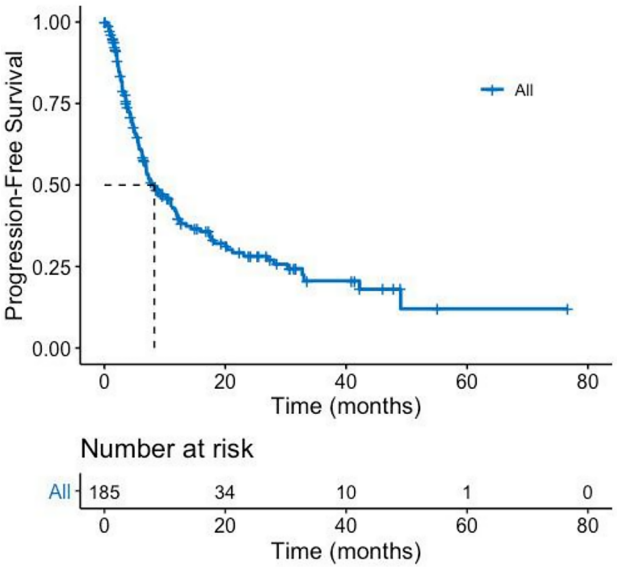

Figure 1. Kaplan-Meier estimates for progression-free survival.

As the cohort consisted of patients with different solid tumors, patients with NSCLC were evaluated separately. Median PFS and OS were 11.0 months (95%CI: 5.0- 17.0) and 29.0 months (95%CI: 20.9-37.1), respectively. Considering the number of previous treatments, median PFS and OS were 28.0 months (95%CI: 6.86-49.14) and not reached for treatment-naïve patients and 5.0 months (95%CI: 3.68-6.32) and 20.0 months (95%CI: 9.69-30.31) for previously treated patients, respectively.

Univariate Cox regression analysis was performed to explore the factors potentially related to PFS and OS. The development of any grade irAEs and have not received prior lines of therapy in the metastatic setting were associated with increased PFS, with an effect *p*-value of <0.001. These two variables and an ECOG PS<2 were associated with increased OS, with an effect *p*-value of <0.005. In the multivariable analysis, ≥1 previous treatment ($p<0.001$) and the development of irAEs ($p<0.001$) remained prognostic factors for PFS.

Table 2. Immune-related adverse events with at least one case grade ≥3.

IrAEs	N=185 (100%)	Grade 3/4	Corticosteroids	Hospitalization
Rash/ pruritus	45 (24.3%)	2 (1.1%)	9 (4.9%)	0 (0%)
Thyroid disturbances	37 (20%)	1 (0.5%)	0 (0%)	1 (0.5%)
Colitis/ diarrhea	21 (11.4%)	6 (3.2%)	4 (2.2%)	4 (2.2%)
Arthritis	16 (8.6%)	1 (0.5%)	4 (2.2%)	0 (0%)
Pneumonitis	9 (4.8%)	2 (1.1%)	8 (4.3%)	2 (1.1%)
Hepatitis	8 (4.3%)	2 (1.1%)	3 (1.6%)	1 (0.5%)
Nephritis	2 (1.1%)	1 (0.5%)	2 (1.1%)	1 (0.5%)
Hypophysitis	1 (0.5%)	1 (0.5%)	0 (0%)	1 (0.5%)
Myositis	1 (0.5%)	1 (0.5%)	1 (0.5%)	1 (0.5%)
Tendinitis	1 (0.5%)	1 (0.5%)	1 (0.5%)	1 (0.5%)
Encephalopathy	1 (0.5%)	1 (0.5%)	1 (0.5%)	1 (0.5%)

Furthermore, the number of prior lines of therapy, development of irAEs, age (<75 years or ≥75 years) and ECOG status were prognostic factors for OS in multivariate analyses (Figures 3 and 4).

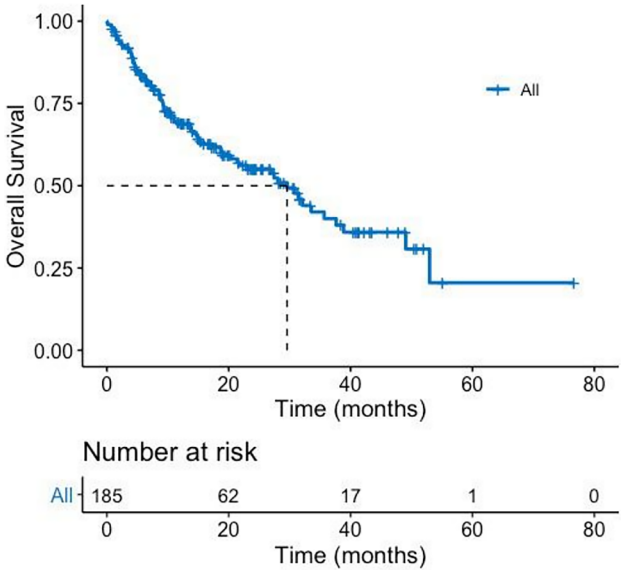

Figure 2. Kaplan-Meier estimates for overall survival.

Variable		N	Hazard ratio	p
Gender	Female	57	Reference	
	Male	100	0.94 (0.60, 1.47)	0.78
Previous Treatment	Treatment Naive	62	Reference	
	≥ 1 Previous treatment	95	3.33 (2.07, 5.36)	<0.001
Treatment Type	Monotherapy	92	Reference	
	Immuno Combined	21	1.84 (0.99, 3.43)	0.05
	Immuno + Chemo	44	1.20 (0.70, 2.03)	0.51
CNS metastasis	No	129	Reference	
	Yes	28	1.21 (0.69, 2.10)	0.51
Age group	< 75 years	116	Reference	
	≥75 years	41	1.43 (0.90, 2.29)	0.13
ECOG	0 or 1	139	Reference	
	2	18	1.55 (0.78, 3.07)	0.21
IRAES	No	78	Reference	
	Yes	79	0.41 (0.26, 0.63)	<0.001

0.5 1 2 5

Progression-Free Survival

Figure 3. Results from Forest Plot models for progression-free survival (PFS).
Legend: CNS: Central nervous system; IRAES: Immune-related adverse events.

Variable		N	Hazard ratio	p
Gender	Female	57	Reference	
	Male	100	0.82 (0.48, 1.39)	0.461
Previous Treatment	Treatment Naive	62	Reference	
	≥ 1 Previous treatment	95	2.01 (1.17, 3.47)	0.011
Treatment Type	Monotherapy	92	Reference	
	Immuno Combined	21	1.56 (0.74, 3.28)	0.237
	Immuno + Chemo	44	0.80 (0.39, 1.62)	0.532
CNS metastasis	No	129	Reference	
	Yes	28	1.03 (0.54, 1.97)	0.929
Age group	< 75 years	116	Reference	
	≥75 years	41	1.73 (1.04, 2.87)	0.035
ECOG	0 or 1	139	Reference	
	2	18	3.23 (1.64, 6.38)	<0.001
IRAES	No	78	Reference	
	Yes	79	0.46 (0.28, 0.77)	0.003

0.5 1 2 5

Overall Survival

Figure 4. Results from Forest Plot models for overall survival (OS).
Legend: CNS: Central nervous system; IRAES: Immune-related adverse events.

DISCUSSION

This real-life retrospective study describes the use of ICIs in a Brazilian tertiary center outside of a clinical trial. In this cohort, most patients presented with NSCLC and melanoma and 40% of the patients have received ICIs in the first line. Our study revealed that 49.7% of patients presented with at least one irAE, and 8.6% developed a grade 3 or 4 event. The permanent discontinuation and hospitalization rates due to irAEs were 2.7% and 7.0%, respectively. A total of 15.1% of patients received supraphysiological dose of steroids for the management of these events, and two patients required biological treatments. Median PFS and OS were 8.26 and 29.6 months, respectively, and the occurrence of irAEs was associated with longer survival outcomes in the overall population.

Despite the heterogeneity regarding the type of tumor and treatment used, patient characteristics were similar to those of other real-world cohorts.[8,9] Moreover, our study demonstrates that uninvestigated subgroups, such as PS=2 (9.7%), older age (≥75 years, 25.9%), and BM (18.9%), represent an important proportion of real-life patients treated with ICIs, which is in accordance with retrospective studies.[9]

Similar to our study, a prospective clinical trial that evaluated pembrolizumab in NSCLC showed a frequency of any adverse events of 71% but a slightly higher frequency of grade ≥3 events (13%).[2] Notably, in that study, the frequency of irAEs was lower than that in our study (17% vs. 49.7%).[2] This divergence might have occurred because irAEs vary according to clinical experience and the criteria used. Other retrospective studies involving four types of cancer demonstrated similar frequencies of irAEs (50.9% and 46.2%) and similar types of the most frequent events (hepatitis, rash, colitis, pneumonitis, and hypothyroidism) as in our study.[10,11] Another Brazilian retrospective cohort study also showed that endocrine and cutaneous AEs were predominant.[12] A retrospective real-world study was conducted on 1.905 patients with advanced lung cancer in China which showed a different spectrum of irAEs, with higher incidence of pneumonitis and lower incidence of gastrointestinal toxicities and arthritis.[13] With regard to irAEs ≥ grade 3/4, real-world data demonstrated a similar incidence (5.8-13.1%).[7,9,11,13] Of note, Shi et al. (2022)[13] and Skribek et al. (2021)[7] described pneumonitis as the most common irAEs ≥ grade 3/4 and Nice et al. (2021),[11] colitis followed by pneumonitis.

Our study showed that only a minor proportion of patients required supraphysiological dose of steroid administration for managing irAEs, which agrees with the results of Skribek et al. (2021)[7] (15.8%). The need for biological treatments was even less frequent, as previously observed.[7,12] The hospitalization incidence due to irAEs was similar to that reported by Nice et al. (2021)[11] (7%); the most common causes also coincided (colitis and pneumonitis). Ahern et al. (2021)[14] reported a higher hospitalization rate than that observed in our study (11%).

Finally, it is important to note that adverse events were not an important cause of treatment discontinuation, possibly because of the predominance of monotherapy. However, the discontinuation rate was divergent from that reported by Bjørnhart et al. (2019)[8] (24% of patients terminated ICI monotherapy due to irAEs); but is in accordance with other studies.[15] We did not observe any deaths in our cohort due to adverse events, similar to the larger cohorts.[16] Nevertheless, Shi et al. (2022)[13] revealed 11 deaths (11/1905, 0.6%) due to irAEs (pneumonitis, liver failure and myocarditis).

The median follow-up period after the first ICI was 12.4 months. The efficacy data were in accordance with those reported in some clinical trials. The KEYNOTE-001 study involving patients with NSCLC and melanoma, the most frequent types of cancer in our cohort, showed a median OS of 22.3 months (95%CI: 17.1 to 32.3 months) in NSCLC treatment-naive patients and 10.5 months (95%CI: 8.6 to 13.2 months) in previously treated NSCLC patients, which are less than those demonstrated in our group.[2] In a melanoma study, the patients exhibited a shorter OS, 23.8 months (95%CI: 20.2-30.4), but a similar PFS of 8.3 months (95%CI: 5.8-11.1).[16] However, real world data have demonstrated shorter median OS and PFS rates. An Italian cohort of patients with NSCLC had a median OS of 11.3 months and a median PFS of 3 months for the pre-treated patients.[17] Another retrospective study of Danish NSCLC patients showed a median OS of 16.1 months and a median PFS of 6.4 months in the general cohort.[8]

In our study, the exploratory analysis suggested that the occurrence of irAEs was associated with longer survival. This finding agrees with those of several retrospective and prospective studies.[13,15,18,19] One possible explanation for this finding is the hypothesis that a more pronounced state of basal immune activation would make patients more likely to present with autoimmune events but would also enhance the antitumor response.[10] Studies that used landmarks or considered time-varying covariates also showed this correlation.[18,20,21] Multiple studies have shown that vitiligo is associated with a lower risk of disease progression and death in patients with melanoma treated with ICIs.[22,23] Maher et al. (2019)[24] found that responders and non-responders to ICIs for urothelial cancer had a differential proclivity for developing irAEs, given the same duration of exposure. Shimozaki et al. (2020)[10] suggested that irAES would be a predictive factor and that the development of multiple irAEs (more than one in the same patient) was correlated with longer OS compared to single irAEs. In addition to irAE development, ECOG PS and line of treatment were associated with outcomes in the multivariate analyses. However, in contrast to previous studies, patients aged ≥75 years had worse OS in our multivariate analyses.[9]

The limitations of our study are its retrospective nature, the heterogeneity and small size of the study population, and the fact that it was based on reference center data. Moreover, patients whose disease progresses or who die have a shorter follow-up period and less treatment exposure, which can impact the association between irAE development and outcomes. Given the retrospective nature of the study, it is possible that grade 1-2 adverse events may have been underestimated, although more severe AEs are likely reported in the patients' charts. However, there are few studies on ICI administration in Brazilian services, and our study illustrates this scenario properly.

CONCLUSION

This study shows that irAEs are frequent in real-world cohorts; most cases are easily manageable and do not require biological treatments. Moreover, they were responsible for a low percentage of hospitalizations and treatment interruptions. Notably, we found an association between irAEs and improved outcomes, which increases the importance of timely diagnosis and a correct management of these adverse events.

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AUTHORS' CONTRIBUTIONS

MPFS: Collection and assembly of data, Conception and design, Data analysis and interpretation, Manuscript writing.

AALP: Data analysis and interpretation, Final approval of manuscript, Provision of study materials or patient.

LNW: Collection and assembly of data, Data analysis and interpretation, Final approval of manuscript.

ACAD: Collection and assembly of data.

RBM: Final approval of manuscript, Provision of study materials or patient.

AK: Final approval of manuscript, Provision of study materials or patient.

IAPM: Final approval of manuscript, Provision of study materials or patient.

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RRM: Data analysis and interpretation, Final approval of manuscript, Provision of study materials or patient.

RBS: Conception and design, Data analysis and interpretation, Final approval of manuscript, Manuscript writing, Provision of study materials or patient.

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