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Immuno-oncology

Association of Immune-Related Adverse Effects and Survival in Solid Tumor Patients Treated with PD1 Inhibitors

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Abstract

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Background The development of immune-related adverse effects (irAEs) can corroborate with the response to immune checkpoint inhibitors (ICIs), including programmed cell death 1 (PD1) inhibitors. However, there is extremely limited data on the association of irAEs with survival in patients who have shown a response to ICIs.

Patients and Methods This study is a retrospective audit of the prospectively collected database of patients who received PD1 inhibitors for advanced solid tumors. Responders were defined as patients who attained the best response of either complete response or partial response. Time-to-event analysis was done using the Kaplan–Meier estimator, and the hazard ratio (HR) was calculated by using Cox proportional model. A point-biserial correlation was used to find out the potential influence of irAEs on overall survival (OS).

Results A total of 155 patients (49% lung cancer, 31% head and neck cancer) who received ICI during the specified period were evaluated for this study. The overall response rate was 19.4% and disease control rate was 43.2%. The median (OS) for patients who developed irAE was 12.3 months (95% confidence interval [CI]: 8.9–15.6), while it was not reached for patients without irAE (HR: 10.5, 95% CI: 1.2–NR, $p = 0.007$). One-year OS for the corresponding group of patients was 53.6% (standard deviation [SD]: 15.6) versus 92.9% (SD: 6.9), respectively. Among responders, 12 (40%) developed at least grade 1 irAE, while among nonresponders, 38 (30.4%) developed irAE ($p = 0.312$).

Conclusions In our study, we found significant improvement in survival of solid tumor patients treated with ICIs who developed irAEs on treatment as compared with those who did not. On specifically analyzing patients who responded to ICIs, there was no difference in OS who developed irAEs versus those who did not. However, this needs to be studied in a larger sample to reach a definite conclusion.

Keywords

- immune checkpoint inhibitors
- responders
- survival outcomes
- immune-related adverse effects
- solid tumors

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Introduction

Employing immunotherapy for the treatment of cancer is not new; the first approved cancer immunotherapy was Bacillus-Calmette-Guerin (BCG) for patients with early bladder cancer in the year 1990.[1] Even long before BCG in 1891, "Coley's toxins," a mixture of live and inactivated *Streptococcus pyogenes* and *Serratia marcescens* achieved responses such as durable complete remission in several malignancies including sarcoma, lymphoma, and testicular carcinoma.[2] Interleukin-2 as a therapeutic measure was approved for metastatic kidney cancer in 1991 and for metastatic melanoma in 1998.[3] The real breakthrough in immuno-oncology came when immune checkpoint inhibitors (ICI) such as cytotoxic T lymphocyte antigen-4 and programmed cell death 1 (PD1) and its ligand (PD-L1) inhibitors entered the landscape.[4] The characterization of immune checkpoint pathways that can be targeted with immune-modulating antibodies led to drug development programs focused on inhibiting the effects of immune checkpoints. Subsequently, ICIs have been approved by the United States Food and Drug Administration in a variety of solid and hematologic malignancies.

Compared with traditional cancer therapies that are directed to kill the tumor cells, ICIs engage the immune system to recognize and eradicate tumor cells. Notable features of ICI therapy include specificity, breadth of response, and memory. These can contribute to complete tumor regressions, often providing more durable clinical outcomes and improved quality of life relative to cytotoxic chemotherapy, molecular targeted therapeutics, and radiation, particularly in metastatic settings. Simultaneously, the unique kinetics of immunotherapy result in different incidences and types of adverse effects, treatment length, and durability of response.[4] Immune-related adverse effects (irAEs) arise due to perturbation of immunological tolerance by ICIs, leading to T cell-mediated damage of self-antigens expressed in the host cells. A meta-analysis of 11,328 patients reported the incidence of irAEs of any grade with anti-PD1 to be ~25%.[5] Also, some studies have shown that the development of irAEs can corroborate with the response to ICIs, keeping up with the similar mechanism of action and effect of irAEs in response to ICIs.[6–8] However, there is very limited data on the association of irAEs with survival in patients who have shown a response to ICIs. Thus, we conducted a retrospective audit of patients who received ICIs and responded to the treatment.

Patients and Methods

Study Population

This study is a retrospective audit of a prospectively collected database of patients who received PD1 inhibitors in any line for metastatic/advanced solid tumors not suitable for curative intent therapy between August 2015 to November 2018 at Tata Memorial Hospital, Mumbai, India. Responders were defined as patients who attained the best response of either complete response (CR) or partial response (PR). Patients received nivolumab at a dose of 3 mg per kilogram or flat 240mg every 2 weeks intravenously or pembrolizumab 200mg every 3 weeks. The treatment was continued until disease progression or unacceptable toxicities. All the patients received single-agent immunotherapy as combination ICI, and cytotoxic chemotherapy was not yet approved in our country at the time of this study. Also, PD-L1 testing was not done, as most of the patients received nivolumab therapy in the second-line or beyond. Steroids were required as a part of the management of irAEs or palliation of symptoms. The study was approved by the institutional review board and ethics committee. The study was conducted as per the Declaration of Helsinki and local guidelines of the Indian Council of Medical Research, New Delhi, India.

Clinical Outcomes

Response assessment was performed using radiological evaluation according to the response evaluation criteria in solid tumors version 1.1. Response assessment was done 8 to 12 weeks after the commencement of ICI or at any symptoms/signs of clinical progression, whichever was earlier. Adverse events during immunotherapy were documented and graded using the common terminology criteria for adverse events, version 4.02. Progression-free survival (PFS) was defined as the interval from the date of starting ICI till the date of progression or death due to any cause if it occurred before disease progression or the last follow-up date, whichever was earlier. Overall survival (OS) was calculated from the date of start of ICI to the date of death. Patients who were still alive were censored at the date of the last contact.

Statistical Analysis

Among responders, baseline characteristics were compared as a function of presence or absence of irAEs using Fisher's exact test or chi-squared test. Time-to-event analysis was done using the Kaplan–Meier estimator, and hazard ratio (HR) was calculated by using Cox proportional model. Swimmer's plot was constructed by using Microsoft Excel 2010. Point-biserial correlation was used to find out the potential influence of irAEs (presence or absence) on the OS. All p-values were based on a two-sided hypothesis with confidence interval (CI) at the 95% level, and $p < 0.05$ was considered statistically significant. All statistical calculations were performed using SPSS statistical software for windows version 20.0 (IBM Corp, Armonk, New York, United States).

Results

A total of 155 patients who received PD1 inhibitors during the specified period were evaluated for this study. The response rate was 19.4% (2 CR and 28 PR). The baseline characteristics of patients who responded to ICI are shown in ►Table 1. The median age of responders was 57 years, with 80% of patients being males and 73% had Eastern Cooperative Oncology Group performance status (ECOG PS) of 0 to 1. Among lung cancer, adenocarcinoma formed 80% of the responding patients without irAEs group, while it was 77.8% in responders with irAEs. All patients with head and

Table 1 Baseline characteristics of the patients included in the study and classified as responders versus nonresponders

Factor	Subfactors	Overall responders, $n = 30$ (%)	Responders with irAEs, $n = 12$ (%)	Responders without irAEs, $n = 18$ (%)	*p*-Value
Age (y)	Median (range)	57 (39–70)	58 (39–68)	57 (42–70)	–
	<60 y	19 (63.3)	07 (58.3)	12 (66.7)	0.712
	≥60 y	11 (36.7)	05 (41.7)	06 (33.3)	
Gender	Female	06 (20.0)	01 (8.3)	05 (27.8)	0.358
	Male	24 (80.0)	11 (91.7)	13 (72.2)	
ECOG PS	0–1	22 (73.3)	9 (75.0)	13 (72.2)	1.000
	2–4	08 (26.7)	3 (25.0)	05 (27.8)	
Line of therapy	1–2	18 (60.0)	7 (58.3)	11 (61.1)	1.000
	3 or more	12 (40.0)	5 (41.7)	07 (38.9)	
BMI (kg/m^2)	<25	19 (63.3)	8 (66.7)	17 (94.4)	1.000
	≥25	10 (33.3)	4 (33.3)	01 (5.6)	
Comorbidities	Present	22 (73.3)	5 (41.7)	17 (94.4)	0.896
	Absent	08 (26.7)	2 (25.0)	6 (75.0)	
Steroids use	No	22 (73.3)	5 (41.7)	17 (94.4)	0.003
	Yes	08 (26.7)	7 (58.3)	01 (5.6)	
Antibiotics use	No	16 (53.3)	5 (41.7)	11 (61.1)	0.296
	Yes	14 (46.7)	7 (58.3)	07 (38.9)	
Site of primary	Lung	14 (46.7)	5 (41.7)	9 (50.0)	0.778
	Head and neck	09 (30.0)	5 (41.7)	4 (22.2)	
	Others	07 (23.3)	2 (16.7)	5 (27.8)	
Smoking	No	25 (83.3)	9 (75.0)	16 (88.9)	0.364
	Yes	5 (16.7)	3 (25.0)	02 (11.1)	

Abbreviations: BMI, body mass index; ECOG PS, Eastern Cooperative Oncology Group performance status; irAEs, immune-related adverse effects.

neck cancer had squamous cell carcinoma histology. ►Fig. 1 shows the consort diagram of this study. All the responders had received nivolumab, and 60% had received ICI in the first or second line. With 37 patients having stable disease as the best response, the disease control rate was 43.2%. The median PFS for responders was 9.5 months (95% CI: 5.6–13.3), while it was 1.7 months (95% CI: 1.4–1.9) for nonresponders (HR: 5.1, 95% CI: 2.8–9.0, $p < 0.001$). One-year PFS for responders was 42.5 (SD: 10.7) and 6.1% (SD: 2.7%) for nonresponders. The corresponding median OS was not reached versus 3.3 months (95% CI: 1.8–4.8) with HR: 5.7, 95% CI: 2.6–12.0, $p < 0.001$ (►Supplementary Fig. S1, available online only). One-year OS for responders was 75.6% (SD: 8.8) versus 26.1% (SD: 5.1). The median follow-up duration of the study patients was 12.9 months (95% CI: 12.1–13.7). ►Supplementary Table S1 (available online only) shows the median and 12-month OS of responders.

Overall 50 patients (32.2%) developed irAEs with grade ¾ toxicities in 23 (14.8%) patients. Among responders, 12 (40%) developed at least grade 1 irAE, while among nonresponders, 38 (30.4%) developed irAE ($p = 0.312$). The cause of death was disease progression in all the patients. No patient expired due to irAEs. Among responders, the median PFS for patients who developed irAE was 8.7 months (95% CI: 5.1–12.4), while it was not reached for patients without irAE ($p = 0.609$). The median OS for patients who developed irAE was 12.3 months (95% CI: 8.9–15.6), while it was not reached for patients without irAE (HR: 10.5, 95% CI: 1.2–NR, $p = 0.007$, ►Fig. 2). One-year OS for the corresponding group of patients was 53.6% (SD: 15.6) versus 92.9% (SD: 6.9), respectively. ►Table 2 shows the comparison of individual irAEs in responders versus nonresponders. Out of total responders ($n = 30$), 14 (46.7%) had lung cancer, while out of all nonresponders ($n = 125$), 62 (49.6%) had lung cancer. The data for patients with lung cancer were analyzed separately, and the median PFS for responding lung cancer patients was 9.5 months (95% CI: 6.9–12.1), while it was 1.6 months (95% CI: 1.3–1.8) for nonresponders. Grade 3/4 irAEs were seen in two (14.3%) responders and seven (11.3%) nonresponder patients of lung cancer.

A point-biserial correlation was run between the OS of responders and the presence or absence of irAEs in the corresponding patients. There were outliers in the data, as assessed by inspection of a boxplot, and these were retained for the analysis. There was homogeneity of variances for the OS and irAEs, as assessed by Levene's test for equality of variances ($p = 0.802$). The OS for the presence or absence of irAEs was normally distributed as assessed by Shapiro–Wilk test ($p > 0.05$). The mean OS was higher in the presence of

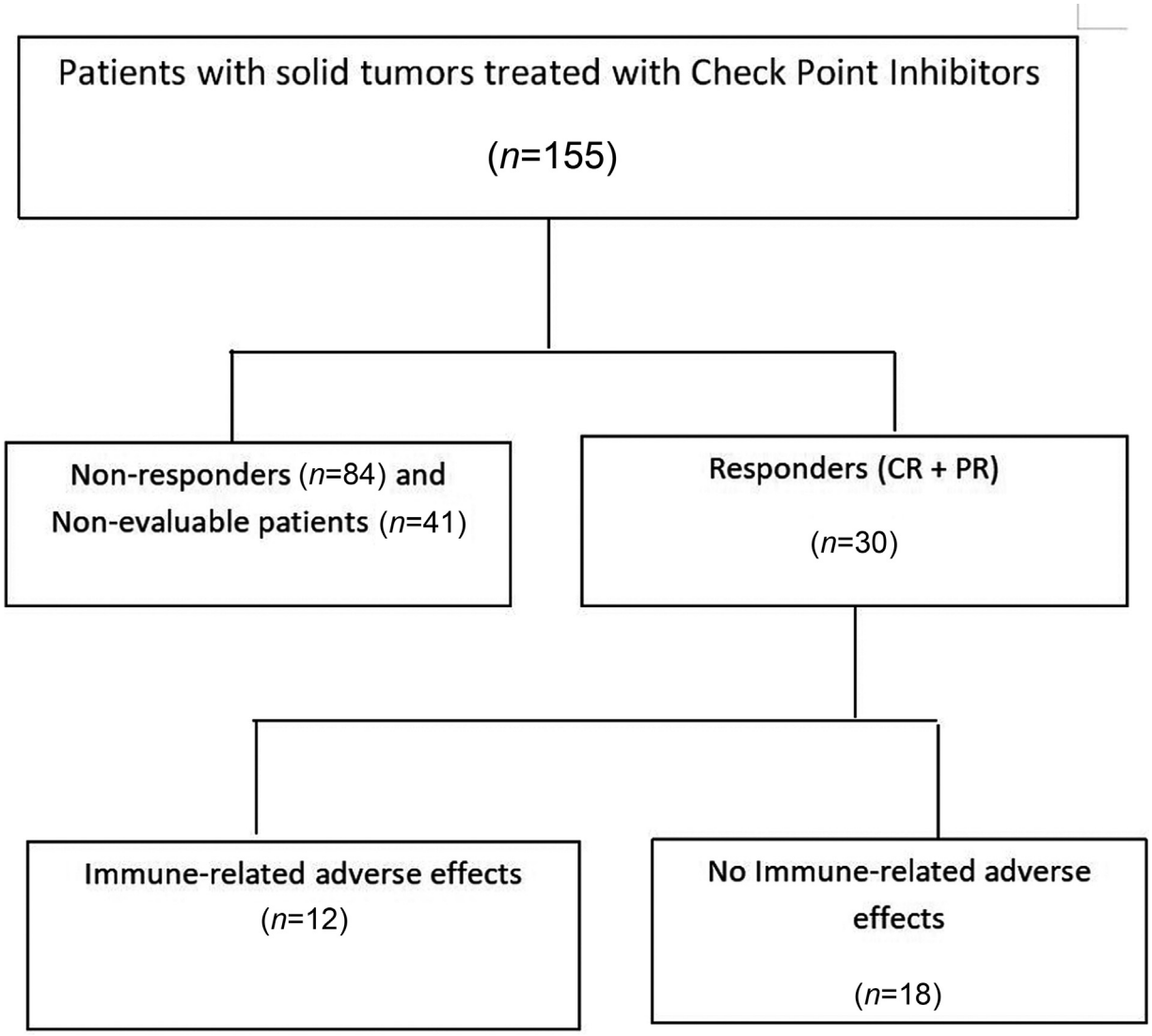

Fig. 1 Consort diagram of the study. Immune-related adverse effects included grade 4 pneumonitis in one patient, grade 3 hepatitis and colitis each in one patient, grade 2 skin rash and nephritis each in two patients, while grade 2 fatigue in four patients. CR, complete response; PR, partial response.

irAEs 6.0 months, 95% CI: 3.1–8.9 as against 5.4 months, 95% CI: 4.4–6.4. However, the coefficient value was 0.141, and it did not reach statistical significance ($p = 0.456$). The presence or absence of irAEs accounted for only 1.9% of the variability in the OS. ►**Supplementary Fig. S2** (available online only) shows the swimmers' plot of responders with and without irAEs.

Univariate analysis with other factors (ECOG PS, steroids, and antibiotics use) did not identify any significant factor in responders. Univariate analysis for gender was not possible as all six female responders in the study had no event for OS in the study duration. The median time of onset of irAEs in responders was 2.3 months (range: 0.5–5.5). The clinical course of the responding patients is depicted in the swimmer's plot in ►**Supplementary Fig. S2** (available online only). The ICI therapy was discontinued in three (10%) responding patients due to irAEs, including grade 4 pneumonitis in one patient, grade 3 hepatitis and colitis each in one patient. Other important irAEs included grade 2 skin rash and nephritis each in two patients, while grade 2 fatigue in four patients. Steroids were required for management of irAEs in 20% ($n = 6$) of the responding patients, while 6.7% ($n = 2$) needed steroids for palliation of symptoms (one each for dyspnea and brain edema related to metastasis).

Discussion

irAEs have been shown to predict survival outcomes in patients with nonsmall cell lung cancer (NSCLC) in patients treated with ICIs.[6–8] However, to our knowledge, no study has addressed this issue in patients with primary other than NSCLC. Also, previous studies have stratified patients based on the occurrence of irAEs only without comparing the data of irAEs in responders and nonresponders. In our study, the primaries included NSCLC and head neck cancer, besides a small proportion of renal cell cancer and urothelial carcinomas. This may explain the differences in results

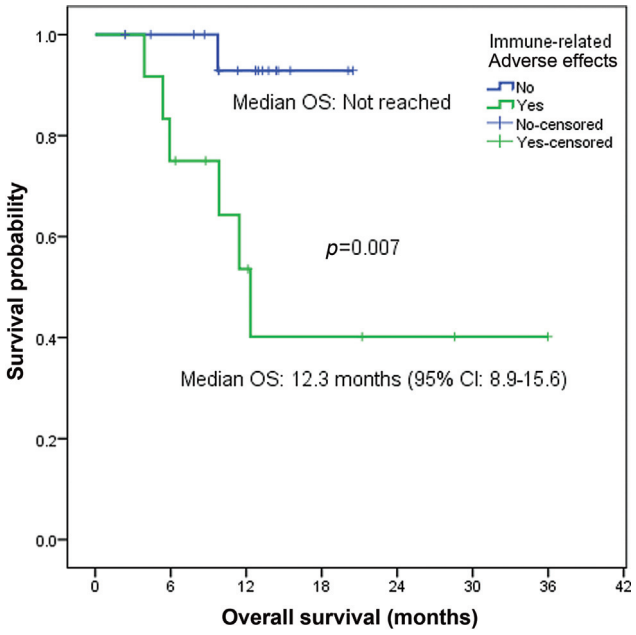

Fig. 2 Kaplan–Meier curve showing overall survival in patients who responded to immune checkpoint inhibitors; blue line shows survival of non-irAEs group versus green line for irAEs group. CI, confidence interval; irAEs, immune-related adverse events; OS, overall survival.

observed in our study. The incidence of irAEs was not statistically different in responders and nonresponders in our study. This is in sharp contrast to a recent study by Akamatsu et al ($n = 106$), which demonstrated that the incidence of irAEs was significantly higher in responders (relative risk 7.85).[9] It would be prudent to note that this study exclusively included patients with NSCLC, and the analysis focused on 23 responders. Besides, our study showed statistically significant longer OS in responders who did not develop irAEs. This suggests that irAEs might overshadow the benefits of immunotherapy probably when they develop early in the course of ICI therapy, like in our study where the medium time to onset of irAEs was 2.5 months. This result is in contrast with the study by Teraoka et al ($n = 43$). They reported that the development of early irAEs (between 2 and 6 weeks of ICI commencement) is associated with better outcomes with nivolumab monotherapy in NSCLC patients.[8] Another study that gave contrasting results was that by Cortellini et al[10] that reported a positive correlation between any grade irAEs and response rates and survival outcomes with anti-PD1 immunotherapy in patients with NSCLC. However, it should be noted that there was no correlation between grade 3/4 irAEs and survival outcomes, which points toward only less severe irAEs signifying the immune activation against tumor cells, while severe irAEs might be counterproductive. The grade 3/4 irAEs in this study was 7.7% as against 14.8% in our study, which might explain the contrasting results. It is prudent to think that patients who were exposed to ICIs for a longer duration might have experienced more irAEs. In a study by Grangeon et al, the authors reported that higher rates of irAEs did not match with higher treatment exposure, which clarifies the above doubt.[11] Also, it was reported in this study that patients who developed early irAEs did not have better survival outcomes, which matches with our study.

Besides the development of irAEs, this study also tried to identify other factors that might be associated with improved survival in responders. However, no such factor could be identified. It should be noted that univariate analysis with gender as a factor could not be done as none of the six female responders developed an event for OS during the study duration. Another important perspective that the authors would like to highlight is that the negative association between ICI therapy and irAEs in responder patients can indicate induction of reactivation of an antitumor immune response without exacerbating latent autoimmunity. This supposed reactivation of an antitumor immune response can influence the OS of the

Table 2 Immune-related adverse effects (irAEs) in responders versus nonresponders to immunotherapy

irAEs	Responders ($n = 30$)		Nonresponders ($n = 125$)	
	Grade 1/2	Grade 3/4	Grade 1/2	Grade 3/4
Rash	2 (6.7)	0	2 (1.6)	0
Fatigue	3 (10.0)	0	13 (10.4)	3 (2.4)
Hepatitis	1 (3.3)	1 (3.3)	4 (3.2)	3 (2.4)
Pneumonitis	0	1 (3.3)	0	6 (4.8)
Colitis	1 (3.3)	1 (3.3)	2 (1.6)	1 (0.8)
Nephritis	1 (3.3)	0	4 (3.2)	0
Adrenal insufficiency	1 (3.3)	0	2 (1.6)	0
Thyroiditis	1 (3.3)	0	5 (4.0)	0
Anorexia	3 (10.0)	0	6 (4.8)	0
Hyponatremia	1 (3.3)	3 (10.0)	1 (0.8)	5 (4.0)
Encephalitis	0	0	1 (0.8)	0
Hypophysitis	0	0	1 (0.8)	0

patients receiving ICIs. Our study suggests that the irAEs are not directly associated with good survival. This indicates that ICI may trigger an antitumor response independently from irAEs. It is important to understand that pathways for irAEs and survival benefit from immunotherapy may differ and are not directly linked to each other. This may be explained by the tumor microenvironment creating the difference and leading to a dampened response to immunotherapy despite irAEs occurring as a result of the effect of immunotherapy on normal cells. Targeting the tumor microenvironment to shift the balance toward the proimmunogenic phase is the main motto of current immunotherapy strategies.[12]

This study has some significant limitations. The most important limitation is small sample size and retrospective nature and data from a single center. However, the real-world settings data are important in day-to-day practice to make appropriate clinical decisions. Another important factor that can create big differences in perceived outcomes is assessing response and classification of an adverse effect as irAE and its grading. Besides, in our study, the analysis has been performed on different cancer types and not a homogeneous cohort of patients. The differences observed in this study can also be because of different ethnicities. There is no study from South-East Asia, and this study adds important data in this important aspect of immunotherapy. Also, this study reinforces the importance of establishing cohorts in centers around the world, which can help in collaboration and data sharing and can ultimately lead to the accumulation of more meaningful data.

Conclusions

In our study, we found significant improvement in survival of solid tumor patients treated with ICIs who developed irAEs on treatment as compared with those who did not. On specifically analyzing patients who responded to ICIs, there was no difference in OS who developed irAEs versus those who did not. However, this needs to be studied in a larger sample to reach a definite conclusion.

Authors' Contributions

Vanita Noronha and Kumar Prabhash conceptualized and designed the manuscript.

Vanita Noronha, Amit Joshi, Vijay Maruti Patil, Amit Joshi, Nandini Menon, and Kumar Prabhash were involved in provision of patients.

Akhil Kapoor, Amit Kumar, Abhishek Mahajan, Amit Janu, and Rajiv Kumar were involved in collection and assembly of data.

Akhil Kapoor, Vanita Noronha, and Kumar Prabhash were involved in data analysis and interpretation.

All authors have contributed in writing of the manuscript.

All the authors gave final approval for the manuscript and were accountable for all aspects of the work.

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The authors or institution did not receive any funding for this research.

Conflicts of Interest

Dr. Prabhash reports grants from Biocon Ltd, Dr. Reddy's Laboratory, Fresenius Kabi India Pvt Ltd, Alkem Labs, Natco Pharma Ltd, BDR Pharmaceuticals Pvt Ltd, and Roche Holding AG, outside the submitted work; all grants paid to the institution. Dr. Noronha reports research grants from Dr. Reddy's Laboratories Inc, Amgen, Sanofi India Ltd., Intas Pharmaceuticals and Astra Zeneca Pharma India Ltd., outside the submitted work. None of the other authors have anything to declare that may be considered as potential competing interests.

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