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Comparative analysis of real-world data of frequent treatment sequences in metastatic prostate cancer

Jiten Jaipuria[a,b,*], Ishleen Kaur[c,d], Mohammad Najmud Doja[e], Tanvir Ahmad[d], Amitabh Singh[a], Sudhir Kumar Rawal[a], Vineet Talwar[f], Girish Sharma[b]

[a]Uro-oncology division, Rajiv Gandhi Cancer Institute and Research Centre, New Delhi, India; [b]Amity Centre for Cancer Epidemiology and Cancer Research, Amity Institute of Biotechnology, Amity University, Noida, India; [c]School of Engineering and Technology, Vivekananda Institute of Professional Studies–Technical Campus, New Delhi, India; [d]Department of Computer Engineering, Jamia Millia Islamia, New Delhi, India; [e]Indian Institute of Information Technology, Sonepat, India; [f]Department of Medical Oncology, Rajiv Gandhi Cancer Institute and Research Centre, New Delhi, India

Abstract

Background: The incidence of prostate cancer is increasing worldwide. A significant proportion of patients develop metastatic disease and are initially prescribed androgen deprivation therapy (ADT). However, subsequent sequences of treatments in real-world settings that may improve overall survival remain an area of active investigation.

Materials and methods: Data were collected from 384 patients presenting with de novo metastatic prostate cancer from 2011 to 2015 at a tertiary cancer center. Patients were categorized into surviving (n = 232) and deceased (n = 152) groups at the end of 3 years. Modified sequence pattern mining techniques (Generalized Sequential Pattern Mining and Sequential Pattern Discovery using Equivalence Classes) were applied to determine the exact order of the most frequent sets of treatments in each group.

Results: Degarelix, as the initial form of ADT, was uniquely in the surviving group. The sequence of ADT followed by abiraterone and docetaxel was uniquely associated with a higher 3-year overall survival. Orchiectomy followed by fosfestrol was found to have a unique niche among surviving patients with a long duration of response to the initial ADT. Patients who received chemotherapy followed by radiotherapy and those who received radiotherapy followed by chemotherapy were found more frequently in the deceased group.

Conclusions: We identified unique treatment sequences among surviving and deceased patients at the end of 3 years. Degarelix should be the preferred form of ADT. Patients who received ADT followed by abiraterone and chemotherapy showed better results. Patients requiring palliative radiation and chemotherapy in any sequence were significantly more frequent in the deceased group, identifying the need to offer such patients the most efficacious agents and to target them in clinical trial design.

Keywords: Hormone therapy; Metastatic prostate cancer; Sequence mining; Survival

1. Introduction

Prostate cancer is the second most common malignancy in men worldwide.[1] Although the incidence of prostate cancer is lower in India than in Western countries, it is increasing every year.[2] Approximately 10%–20% of patients are diagnosed with metastatic stage cancer, and this proportion is higher in Indian patients.[3]

Androgen deprivation therapy (ADT, implying orchidectomy, degarelix, or luteinizing hormone-releasing hormone [LHRH] agonists with or without first generation antiandrogen) remains the pivotal treatment for metastatic prostate cancer; however, patients become hormone-refractory over time. These patients may be subsequently sequentially treated with other options such as chemotherapy and novel antiandrogens. However, many pivotal trials have shown that introducing these treatments upfront with ADT increases the overall survival (OS). Thus, the present guidelines recommend the coadministration of either docetaxel or a novel antiandrogen (apalutamide, abiraterone, or enzalutamide) with the initial ADT or even a triplet combination.[4] However, many patients either fail to adhere to prescribed combination treatments or continue to be treated conventionally.[5,6] Thus, there remains a notable chasm between trials and real-world practice. In addition, trials have concluded that different cancer drugs may share cross-resistance, especially novel antiandrogens.[7] Thus, there is an unmet need for data on the consequences of different treatment sequences, which are expected to have implications irrespective of whether patients are treated using conventional or modern approaches. Furthermore, although trials have yet to resolve the equipoise between chemotherapy and novel antiandrogens as an initial choice, many factors dictate the choice of therapy in real-world settings. Thus, data on the consequences of real-world treatment choices have the potential to unmask novel findings.

Attempts have been made to predict survival outcomes in patients with metastatic disease based on the initial choice of treatment agents or baseline patient characteristics.[8] It has been previously recognized that data mining techniques perform better than conventional statistical methods for discriminating survival outcomes in metastatic prostate cancer.[9] This study applies this knowledge to analyze different treatment sequences in detail,

*Corresponding Author: Jiten Jaipuria, Uro-oncology Division, Rajiv Gandhi Cancer Institute and Research Centre, Rohini, Sector 5, New Delhi, 110085, India. E-mail address: jitenjaipuria@yahoo.co.in (J. Jaipuria).

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Jiten Jaipuria and Ishleen Kaur contributed equally.

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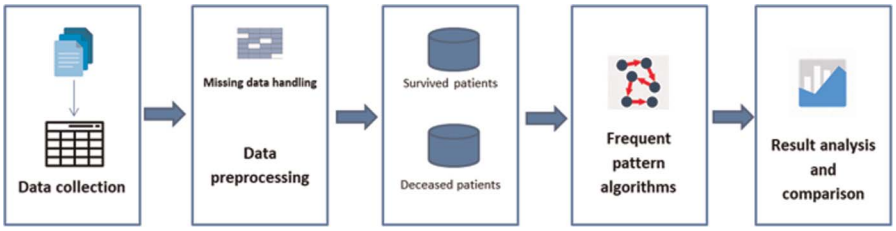

Figure 1. Schematic diagram of overall study methodology.

aiming to identify specific sequences associated with improved OS. The purpose of the study was to identify the distinguishing set of treatment sequences found in the 2 groups of patients—"surviving" and "deceased," after being diagnosed with de novo metastatic prostate cancer, and interpret it in a clinical context. We deviated from a conventional statistical approach and used two popular sequence mining techniques, Generalized Sequential Pattern Mining (GSP) and Sequential Pattern Discovery using Equivalence Classes (SPADE), to extract frequent sequences of treatments found in both groups.[10,11] This alternative approach was necessary because conventional statistical techniques have limitations when dealing with data that involve sequential treatments with each step dictated by numerous confounding factors. We hypothesized that the observed differences in treatment sequences between the groups could have prognostic and therapeutic implications. To the best of our knowledge, distinguishing sets of treatment sequences using real-world data in surviving and deceased groups of patients has not been explored in previous studies.

2. Materials and methods

2.1. Data collection

Figure 1 illustrates the overall followed methodology. After ethics committee approval, data were collected from a high-volume tertiary cancer care center in India for all Indian patients diagnosed with de novo metastatic prostate cancer between 2011 and 2015 and treated outside clinical trials (to reflect the real-world situation and gain unique insights). Individual case files were retrieved, and the data set was compiled manually. Most of the patients (99%) had adenocarcinoma histology. While most patients (73%) had bone metastasis, a large number (21%) had nodal metastasis, and only a few (6%) had visceral metastasis at presentation. Treatment lines were recorded for each patient, including ADT, chemotherapy, secondary androgen-manipulating agents (abiraterone, enzalutamide, and fosfestrol), and palliative radiotherapy. For ADT, further particulars, including degarelix, bilateral orchiectomy (surgical hormonotherapy), and LHRH agonists, were recorded. We excluded patients who developed metastatic disease after initial radical treatment for localized prostate cancer and those who did not receive hormonal therapy as their first treatment (seen infrequently).

The primary outcome was 3-year OS (defined as the time from the date of diagnosis of metastatic prostate cancer until death due to any cause or the last date of follow-up, if alive).

2.2. Data preprocessing

The data collected for the study included the sequence of up to 4 treatment lines administered to the patients in the 3 years after diagnosis. Patients with missing treatment details or those who had opted out of the hospital before 3 years were excluded. The final data set comprised 384 patients. The preprocessed data were categorized into 232 surviving (60.41%) and 152 deceased (39.59%) patients, based on their survival outcomes.

Table 1 presents the treatments used in this study. We defined a minimum of 3 months of administration of a particular treatment to be a part of a sequence. As is evident from Table 1, almost 33% of the patients were not given any further treatment beyond the first-line treatment. Chemotherapy included docetaxel unless otherwise specified. Less than 10% of the patients received up to 4 lines of treatment during the study period.

Patients receiving multiple lines of therapy had similar 3-year OS to patients who had good response to ADT alone, with a chi-square test statistic (χ^2) = 0.1005 and p = 0.751 (using IBM SPSS v 26; IBM Corp, Armonk, NY). For patients receiving other treatments after the initial ADT, we subsequently performed frequent pattern mining.

The baseline characteristics of the surviving and deceased groups are presented in Table 2. The surviving and deceased groups had similar age, prostate-specific antigen (PSA) levels at diagnosis, Gleason grades, and T stages. However, nadir PSA levels were significantly lower in the surviving group.

Table 1

Treatment data.

Treatment sequence	Treatment	Patients, n (%)
First treatment	Degarelix	21 (5.4)
	LHRH agonists	132 (34.37)
	Orchiectomy	231 (60.15)
Second treatment	Fosfestrol	60 (15.625)
	Enzalutamide	1 (0.26)
	Abiraterone	41 (10.677)
	Chemotherapy	65 (16.93)
	LHRH agonists	4 (1.04)
	Orchiectomy	10 (2.604)
	Radiotherapy	77 (20.05)
	No treatment	125 (32.55)
Third treatment	Chemotherapy	35 (9.15)
	Abiraterone	41 (10.677)
	Degarelix	1 (0.26)
	Fosfestrol	19 (4.95)
	LHRH agonists	2 (0.52)
	Orchiectomy	3 (0.78)
	Radiotherapy	24 (6.25)
	Enzalutamide	1 (0.26)
	No treatment	258 (67.19)
Fourth treatment	No treatment	346 (0.104)
	Abiraterone	14 (3.64)
	Chemotherapy (cabazitaxel)	14 (3.64)
	Fosfestrol	4 (1.04)
	Radiotherapy	6 (1.56)

LHRH = luteinizing hormone-releasing hormone.

Table 2

Baseline characteristics of survived and deceased group.

	Survived group, n = 232	Deceased group, n = 152
Mean age, yr	65.27	67
Mean PSA at diagnosis, ng/mL	418.66	548.45
Mean nadir PSA, ng/mL	2.977	49.45
Mode Gleason score	8	8
Mode T stage	4	4

PSA = prostate-specific antigen.

2.3. Frequent pattern mining algorithms

Sequence mining or sequential pattern mining refers to the identification of a repeatedly occurring set of subsequences to discover useful, novel, and/or unexpected patterns. To analyze the sequence of treatments for both the surviving and deceased groups, 2 popular sequence mining algorithms were applied to the data: GSP[10] and SPADE.[11] Generalized Sequential Pattern Mining involves level wise mining, whereas SPADE follows a vertical approach. To acquire a good number of frequent sequences, a support value of 0.05 was used for both the algorithms and for both groups; that is, the treatment sequences with a support less than 0.05 were pruned in each of the surviving and deceased datasets. The algorithms were modified to capture treatment sequences in exact order. The exact order constraint, also known as the no-gap constraint, allows the algorithm to consider only instances with no intermediate treatment between them.[12] Thus, if treatment C is given to the patient after treatments A and B, then the sequences considered for the analysis are shown in Figure 2. A ➔ C was not considered in the study, as intermediate treatments may not have a significant effect on the outcome. In addition, this study aimed to identify the exact order of treatment sequences to be administered to patients with improved OS.

For illustration, the original GSP algorithm and its modification is explained in Appendix A (see Supplemental Digital Content, http://links.lww.com/CURRUROL/A42).

3. Results

The frequent pattern mining algorithms were implemented in Java. Both GSP and SPADE yielded the same results, and a common result analysis was performed for both algorithms. Table 3 lists the frequent sequences found in both the surviving and deceased groups. Only one 1-length sequence, degarelix, was uniquely evident in the surviving group. All remaining frequent sequences with a length of one were removed from the analysis, as they were common to both the surviving and deceased groups, making comparative analysis irrelevant. The distinguishing set of sequences in each group is highlighted and italicized in Table 3. The sequence of ADT followed by abiraterone and docetaxel was uniquely associated with a higher 3-year OS. Orchiectomy followed by fosfestrol was found to have a unique niche among surviving patients with a long duration of response to the initial ADT. Patients who received chemotherapy followed by radiotherapy and those who received radiotherapy followed by chemotherapy were more frequently in the deceased group. The distinguished surviving sequences are visually represented using a digraph using GraphViz[13] in Figure 3. Thicker edges represent higher support values for the sequences. Support values decrease moving down the sequence, except for abiraterone ➔ chemotherapy, which was also evident separately; thus, they are represented with different outlines. For a better illustration, a graphical representation of the sequences (with at least two sequences in the recommended treatment procedures) in both the surviving and deceased groups is shown in Figure 4.

Figure 2. Diagrammatic representation of exact order sequence analysis.

The results were evaluated statistically to confirm the validity of the obtained sequences. All the sequences found to be relevant in either the surviving or deceased groups were checked for their statistical relationship with the class (surviving/deceased). The level of significance was set at $p < 0.05$. Table 4 lists the p values computed for each sequence in the entire dataset.

4. Discussion

4.1. Rationale

In this study, treatment sequences for metastatic prostate cancer were analyzed using machine learning tools to explore cancer management based on real-world determinants drawing from our previous experience.[14] Androgen deprivation therapy, docetaxel, and novel antiandrogens have been recommended as the standard of care in doublet or triplet combinations for the treatment of metastatic hormone-sensitive prostate cancer.[4] However, the findings from our study remain relevant because the analysis of large real-world datasets from the United States revealed that even in 2020, most patients received ADT monotherapy as first-line therapy.[5] Even with correctly prescribed combination therapy, compliance with treatment remains a major concern in a recent study observing nonadherence to novel-antiandrogens in more than 40% of patients with advanced prostate cancer in North America.[6] In the authors' personal experience, the situation in India is no different; thus, clinicians worldwide stand to gain useful insights from our study findings.

Table 3

Treatment sequence comparison in survived and deceased groups.

Deceased group	Survived group
Fosfestrol ➔ abiraterone	***Degarelix***
Orchiectomy ➔ abiraterone	Fosfestrol ➔ abiraterone
Chemo ➔ abiraterone	Orchiectomy ➔ abiraterone
LHRH agonist ➔ abiraterone	Chemo ➔ abiraterone
Fosfestrol ➔ chemo	***Abiraterone ➔ chemo***
LHRH agonist ➔ fosfestrol	LHRH agonist ➔ abiraterone
Orchiectomy ➔ radiotherapy	***Orchiectomy ➔ fosfestrol***
Orchiectomy ➔ chemo	Fosfestrol ➔ chemo
Chemo ➔ radiotherapy	LHRH agonist ➔ fosfestrol
Radiotherapy ➔ chemo	Orchiectomy ➔ radiotherapy
LHRH agonist ➔ radiotherapy	Orchiectomy ➔ chemo
LHRH agonist ➔ chemo	LHRH agonist ➔ radiotherapy
	LHRH agonist ➔ chemo
	Orchiectomy ➔ abiraterone ➔ chemo

Statistically significant sequences are bolded and italicized.
chemo = chemotherapy; LHRH = luteinizing hormone-releasing hormone.

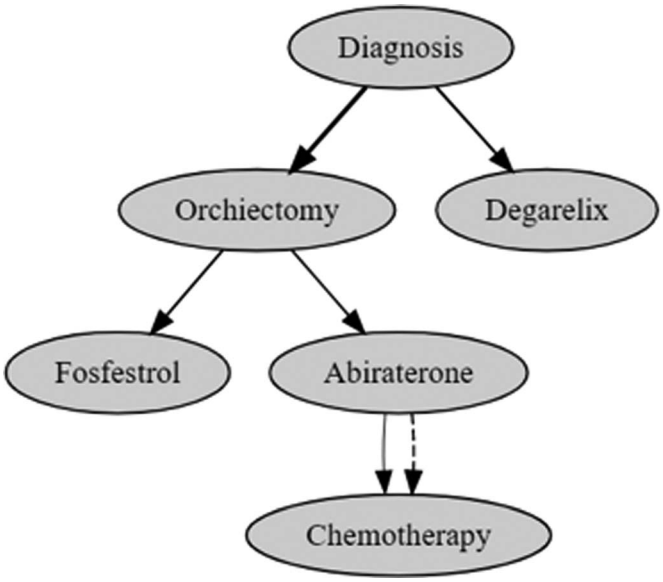

Figure 3. Diagraph showing distinguishing set of sequences found in the survived subgroup.

Our article refrains from a conventional statistical approach, in which baseline clinical and demographic characteristics are identified and univariate and multivariate analyses are performed. This approach is incapable of analyzing the impact of sequential treatments, where baseline patient characteristics change with each step as the patient progresses through their cancer journey. For example, even if we know from conventional statistics that a lower nadir PSA is associated with superior outcomes, this provides no information about the treatment the patient received. We chose a different statistical approach in which such factors do not matter and treatment choices and outcomes are principally analyzed, capturing the entire treatment journey as a snapshot. If we assume equivalence between different ADT options, other treatment options (e.g., novel antiandrogens vs. chemotherapy), or their sequencing, sequence pattern techniques should not reveal any distinguishing sequence set. However, our real-world data analysis revealed clear and unique patterns. To the best of our knowledge, this is a first of its kind analysis not yet reported in the prostate cancer literature. However, although modern artificial intelligence and machine learning techniques are powerful and can handle complex datasets in unique ways, the results must be interpreted carefully in the correct context.

4.2. Principal findings and clinical context

We observed that patients receiving multiple lines of therapy had a 3-year OS similar to that of patients who had a good response to ADT alone. This may be indirect evidence that subsequent lines of treatment meaningfully improve the OS, such that patients with a more aggressive or higher burden of disease (who are expected to be given multiple lines of treatment) experience a 3-year OS similar to those with a less aggressive or metastatic burden of disease (who are expected to do well with ADT alone).

Table 3 provides an analysis of both surviving and deceased groups. Although most of the treatment sequences were common to both clusters, some treatment sequences were exceptional for either group. First, ADT via degarelix was uniquely in surviving patients. Its prominence in the surviving group indicates that this treatment leads to improved OS, although only 5.4% received degarelix (Table 1) as the first treatment. Degarelix has been proven to achieve quicker suppression of PSA levels[15] and higher progression-free survival and OS rates than other forms of ADT.[16] In a real-world setting in India, patients often do not choose degarelix because of its cost and the need for frequent clinic visits. Patients coming from far distances from the hospital also tended to prefer longer-acting ADT agents.

Another treatment sequence evident in the surviving group was abiraterone ➔ chemotherapy and orchiectomy ➔ abiraterone ➔ chemotherapy. Although orchiectomy ➔ abiraterone was common in both groups, its use in combination with chemotherapy was evident only in the surviving group. Multiple investigators have compared the sequence of abiraterone ➔ chemotherapy and chemotherapy ➔ abiraterone with equivocal or conflicting results favoring initial treatment with abiraterone.[17,18] However, a systematic review observed cross-resistance between docetaxel and abiraterone and a generally higher proportion of more than 50% PSA decline for the abiraterone ➔ chemotherapy sequence.[19] Abiraterone was the first novel antiandrogen to be approved in India, and its cost is lower than that of other agents. Recently, a trial showed that a lower dose of 250 mg with food is oncologically noninferior to the conventional 1000-mg empty stomach dose in patients with castration-resistant prostate cancer (CRPC).[20] This, combined with its low toxicity profile, further improves its attractiveness compared with chemotherapy, making it the default real-world choice of many Indian oncologists.[21] Until more data are obtained to support these results, these treatment sequences should be considered when treating patients.

In addition, the treatment combination of chemotherapy and radiotherapy (i.e., chemotherapy ➔ radiotherapy and radiotherapy ➔ chemotherapy) was found evident only in the deceased group, which can be explained by the bias of poor-risk patients with more advanced disease receiving palliative radiation for bone metastasis or rectal invasion (this obviously excludes patients given palliative radiation to the prostate for oligometastatic disease). This finding identifies a unique subgroup of patients with poor 3-year OS in which the most efficacious agents should be prioritized, and trials targeting this patient subgroup are likely to reach their endpoints more quickly. This finding has a similar potential application in trial design, for patients with more than 10 months PSA doubling

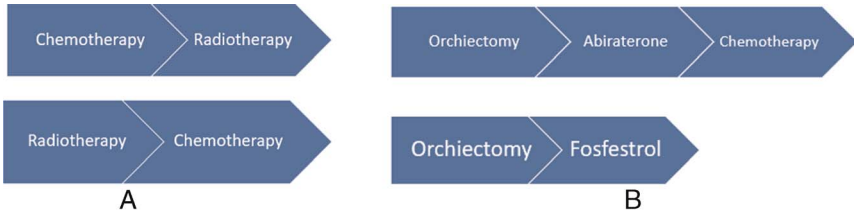

Figure 4. Distinguishing treatment sequences (more than 1 length) for (A) deceased group and (B) surviving group.

Table 4

***p* values of important treatment sequences.**

Treatment sequence	*p*
Chemotherapy → radiotherapy	**0.0271**
Radiotherapy → chemotherapy	**0.0056**
Degarelix	0.8415
Abiraterone → chemotherapy	**0.0009**
Orchiectomy → fosfestrol	**0.0107**
Orchiectomy → abiraterone → chemotherapy	0.7057

Statistically significant sequences are bolded and italicized.

time in trials for nonmetastatic CRPC, or patients with a higher metastatic disease burden in trials for de novo metastatic prostate cancer. Recently, trials have shown that cabazitaxel may be a better choice than novel antiandrogens for patients with metastatic CRPC and poor-risk features such as visceral metastasis.[22] In addition, cabazitaxel may be a better choice than switching between novel antiandrogens in patients with postprogressive metastatic CRPC on docetaxel and a novel antiandrogen.[23] Finally, the TheraP trial identified that leutetium-177 prostate specific membrane antigen therapy may be a more efficacious choice for those in whom cabazitaxel is deemed the next appropriate choice.[24]

Finally, the treatment sequence of orchiectomy followed by fosfestrol is also exceptional only the surviving group, which can be explained by bias due to good-risk patients being offered this drug after PSA-only progression with a prolonged PSA doubling time. Fosfestrol remains a popular choice for many old practicing urologists, and our study highlights a unique subset of patients in whom it may remain an option, although we recommend better agents with more robust survival data for other situations.

All treating clinicians involved in the study agreed with the validity of the frequent patterns of treatment sequences. Ascertaining real-world validity is an essential element discussed in the practice of artificial intelligence and social good.[25]

4.3. Limitations

Table 4 shows the conventional statistically significant results of the sequences. All of the sequences were found to be significant in the overall dataset, except for the degarelix and orchiectomy → abiraterone → chemotherapy sequence. The reason the orchiectomy → abiraterone → chemotherapy lacked significance may be due to the length of the sequence of treatments because as depicted in Table 1, more than 67% of the patients in our study did not receive more than 2 treatments. Thus, while this was not significant in the overall dataset, but its significance was captured in the surviving group. Similarly, few patients received degarelix in our dataset.

5. Conclusions

Metastatic prostate cancer is a heterogeneous disease with variable OS. This study offers evidence-based insights using real-world data and decisions made outside clinical trials. Degarelix was uniquely found frequently in the surviving group and should be the preferred form of ADT. The sequence of abiraterone → chemotherapy (docetaxel) was also found more frequently in the surviving group and should be preferred in the clinical situation of equipoise. Some patients responded well to ADT alone and continued to respond well to fosfestrol in the event of PSA progression, thus identifying a unique niche for this drug. Patients who received chemotherapy followed by palliative radiotherapy and palliative radiotherapy followed by chemotherapy were more frequent in the deceased group, identifying the need to offer such patients the most efficacious agents and to target them in clinical trial design.

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Statement of ethics

Ethical approval was granted by the institutional review board of the Rajiv Gandhi Cancer Institute and Research Centre, New Delhi, India (Res/SCM/43/2020/119). Data were collected in accordance with the hospital policies. All procedures performed in this study involving human participants were in accordance with the ethical standards of the institutional and national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. Because of the retrospective nature of study and the use of anonymized records, need to obtain informed consent from study participants was waived off.

Conflict of interest statement

No conflict of interest has been declared by the author.

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None.

Author contributions

JJ: Participated in research design, writing of the paper, data analysis;
IK: Participated in research design, writing of the paper, contributed new analytic tools, data analysis;
MND: Contributed new reagents or analytic tools, performance of the research;
TA: Participated in performance of the research;
AS, SKR, VT, GS: Participated in research design.

Data availability

The datasets generated during and/or analyzed during the current study are not publicly available, but are available from the corresponding author on reasonable request.

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