

A secondary data analysis of qualitative study of individualized treatment regimen for North Indians living with human immunodeficiency virus-1

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Research

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Abstract

Background

A correlation between the CD4 counts and viral loads of HIV-1 infected North Indian patients with first line ART was reported. The follow up of fifty-seven patients were conducted after a confirmation genotypic test. The secondary data analysis was done on the data available to observe the correlation between the CD4 counts and viral loads (markers of clinical outcome) of HIV-1 Subtype C infected North Indian patients.

Methods

After analysis of the drug resistance mutations in individual patients through the drug resistance database, Stanford University, the data of resistance associated drugs, CD4 counts, viral load of individuals were compiled and analysed using Microsoft Excel 2016 and SPSS Version 22. Normality of data was checked by Shapiro-Wilk test ($p < 0.05$).

Results

Starting and study end point data on CD4 count, viral load and drug resistance pattern associated with multiple first line ART was available for 24 North Indian patients. Starting and study end point data on CD4 count and drug resistance pattern associated with multiple first line ART was available for 33 North Indian patients.

Conclusion

Our findings are categorically indicative that policy recommendation to provide tailor-made individualized regimen based on molecular drug resistance testing to HIV patients under AIDS control program requires robust evidence before implementation.

Introduction

The first line antiretroviral therapy regimen was implemented by National AIDS Control Organization sponsored ART centre in India in the year 2004 [1]. It is comprised of two nucleoside reverse transcriptase inhibitors (NRTIs) and a non-nucleoside reverse transcriptase inhibitor (NNRTIs) [2, 3]. If the patients fail the first line ART, they were put on second line ART like Atazanavir, Ritonavir, etc. The national program in India has supported the clinical and immunological monitoring of first line ART patients by routine CD4 count and viral load monitoring [3]. The 90-90-90 Strategy can be successful by implementing CD4 counts, viral load and genotyping to assess HIV drug resistance in a national program [4]. The harrowing time spent by patients with drug resistance mutations without genotyping test can have a significant

impact on the life of the patients [5]. Genotyping is the most common method of gene sequencing for the detection of HIV drug resistance mutations [6] Commercial and in-house methods are widely used for the genotypic test of HIV-1 drug resistance [7].

Genotypic drug resistance testing could be useful in patients who were initiated with first line ART and identify PLHIV with virological failure. Based on genotypic drug resistance testing, appropriate regimen can be initiated during the period of treatment. WHO's report on nationally representative surveys on pre-treatment HIV drug resistance (PDR) between 2014 and 2016 suggests greater than 10% PDR to NNRTI was reported by 6 out of 11 countries. The estimated prevalence of NNRTI resistance among all patients on ART varied between 5% and 28%. At present, antiretroviral treatment (ART) failure is monitored through CD4 counts, viral load and clinical profile by National AIDS Control Programme in India. Currently, drug resistance testing by molecular methods is not routinely done in the initiation of treatment or monitoring of response to ART. The study suggests, the broader scale implementation research for the use of the tailor-made suitable drugs after an individualized genotypic test in national programs in India.

Materials And Methods

Study design, treatment Policy and collection of samples

At antiretroviral therapy centre, Sarojini Naidu Medical College, Agra, North India, 57 patients on the first line antiretroviral therapy between December 2009 to November 2016 were tested for drug resistance by genotypic study. Patients were followed up till August 2019. All patient's information was collected using the own designed patient information leaflet [8]. The selection of patients for genotyping was based on either of CD4 counts (<350 cubic/mm), WHO clinical staging of HIV/AIDS and viral load (≥ 1000 copies/ml). This is a secondary analysis of de-identified data of 57 patients on CD4 count, viral load and drug resistance pattern. Data of all patients on HIV drug resistance, pre-treatment and interim CD4 count and viral load was not available. Out of 57 patients, 51 were found to be drug resistant. Data on pre-treatment and study end point CD4 count, viral load and HIV drug resistance were available for 24 patients while only starting CD4 count with viral load and study end point CD4 count of 33 patients was available.

Viral load and genotyping analysis

Viral load was done by using the Abbott automated m2000rt instrument. The genotyping was performed for first line ART failure at the National Institute for Research in Tuberculosis, Chennai by using the WHO dried blood spot protocol 2010. The modified polymerase reaction conditions and primers of the WHO dried blood spot protocol 2010 was reported. The sequenced product of 935bp PR and 750bp RT gene fragment of HIV-1 was taken for genotyping. The drug resistance mutation of each sample was identified and interpreted using the Stanford HIV drug resistance database.

(http://hivdb.stanford.edu/pages/algs/sierra_sequence.html) and was already reported [10].

Statistical analysis and interpretation of first line ART failure drugs

After analysis of the drug resistance mutations in individual patients, the data of individuals were compiled and analysed using Microsoft Excel 2016 and SPSS Version 22. Normality of data was checked by Shapiro-Wilk test ($p < 0.05$). It showed that CD4 count and viral load are not normally distributed. Frequency analysis was done when resistance was found in more than one first line anti-retroviral drug. Wilcoxon signed rank test was used for hypothesis testing for CD4 count and viral load.

Results

All 57 HIV-1 infected North Indian patients were tested by genotyping and the drug resistance mutations were analysed in individual patients. Fifty-one North Indian patients were detected with drug resistance mutations (DRMs) associated with NRTIs and NNRTIs. CD4 count and viral load were considered as prognostic markers to assess treatment outcome. The North Indian patients received the mentioned drugs in different regimens as per their clinical profile and adverse drug events during the treatment duration.

Data on pre-treatment and study end point CD4 count, viral load and HIV drug resistance were available for 24 North Indian patients. All 24 North Indian patients showed resistance to one or more than one first line anti retro viral drugs [Table 1 (a)]. Out of 24 North Indian patients, three patients died during the treatment. One of them had decreased CD4 count and viral load both. CD4 count decreased and viral load increased for rest two patients. In the remaining 21 North Indian patients, in the presence of drug resistance, both CD4 count and viral load declined in two patients while CD4 count decreased and viral load increased in 7 North Indian patients. Both CD4 count and viral load increased in 3 North Indian patients, whereas CD4 increase and viral load decrease was observed in 12 North Indian patients despite the drug resistance. Out of 24, 16 North Indian patients were shifted on a second-line regimen after first line HIV drug resistance was detected in them. One patient was started with AL/ATV/RTV. But the patient died during the course of treatment. There was a decline in both CD4 count and viral load. Two North Indian patients were started with SL/ATV/RTV, 8 North Indian patients with TL/ATV/RTV and 5 North Indian patients with ZL/ATV/RT. There was no significant difference between starting and end point CD4 count ('p' value 0.391) as well as viral load ('p' value 0.616).

Table 1 (a): Drug resistance pattern of patients

Sr. No.	Drugs	First line ART failure drugs	No. of patients	CD4 count at DSA	End point CD4 count	Viral load at DSA	End point viral load	Second line regimen	Total treatment duration (Months)	Adherence (%)	Status of the patient	Remark
1	Abacavir, Lamivudine Nevirapine, Tenofovir Efavirenz	Abacavir, Lamivudine Nevirapine, Tenofovir Efavirenz	1	134	20	371277	16842	AL/ATV/RTV	26.6	96.27	Dead	CD4 decrease Viral load decrease
2	Stavudine, Lamivudine Nevirapine, Zidovudine Tenofovir, Efavirenz	Stavudine, Lamivudine, Nevirapine, Tenofovir, Efavirenz	1	271	218	5427	40426	No	48.28	99.31	Alive	CD4 decrease Viral load increase
3	Stavudine, Lamivudine, Nevirapine, Tenofovir, Efavirenz	Lamivudine, Nevirapine, Efavirenz	1	64	522	7964	TND	ZL/A TV/RTV	80.29	98.71	Alive	CD4 increase Viral load decrease
4	Stavudine, Lamivudine, Nevirapine, Tenofovir, Efavirenz	Lamivudine, Tenofovir, Efavirenz, Nevirapine	1	53	102	1802	24391	No	53.1	98.7	Alive	CD4 increase Viral load increase
5	Stavudine, Lamivudine, Nevirapine, Zidovudine, Efavirenz	Nevirapine, Efavirenz	1	110	268	36177	<20	No	62.26	99.5	Alive	CD4 increase Viral load decrease
6	Tenofovir, Lamivudine, Efavirenz	Lamivudine, Nevirapine, Efavirenz	1	202	218	22854	336119	ZL/A TV/RTV	15.19	94.4	Alive	CD4 increase Viral load increase
		Efavirenz	1	83	279	373829	43	SL/A TV/RTV	16	95.17	Alive	CD4 increase Viral load decrease
			1	121	198	89339	12891	No	18.11	95.63	Alive	CD4 Increase Viral load decrease
7	Tenofovir, Lamivudine, Efavirenz, Nevirapine	Lamivudine, Nevirapine, Efavirenz	1	141	78	6353	670719	ZL/A TV/RTV	42.19	97.86	Dead	CD4 Decrease Viral load increase
			1	103	148	519326	537350	ZL/A TV/RTV	39.23	98.8	Alive	CD4 increase Viral load increase
		Nevirapine, Efavirenz	1	133	192	2066	1189	ZL/A TV/RTV	29.13	98.45	Alive	CD4 increase Viral load decrease
8	Tenofovir, Lamivudine, Nevirapine, Zidovudine, Efavirenz	Zidovudine, Lamivudine, Nevirapine, Efavirenz	1	143	192	465426	2256	TL/A TV/RTV	41.5	98.38	Alive	CD4 increase Viral load decrease
9	Zidovudine, Lamivudine, Efavirenz, Stavudine, Nevirapine, Tenofovir	Zidovudine, Lamivudine, Tenofovir, Stavudine, Efavirenz, Nevirapine	1	83	49	9983	11847	No	72.2	99.14	Dead	CD4 decrease Viral load increase
10	Zidovudine, Lamivudine, Efavirenz, Tenofovir	Zidovudine, Lamivudine, Efavirenz, Tenofovir	1	295	82	2950	<20	SL/A TV/RTV	41.5	93.59	Alive	CD4 decrease Viral load decrease
		Zidovudine, Lamivudine, Efavirenz, Nevirapine	1	204	223	62572	60	TL/A TV/RTV	57.7	98.19	Alive	CD4 increase Viral load decrease
12	Zidovudine, Lamivudine, Nevirapine	Zidovudine, Lamivudine	1	137	90	44125	286866	TL/A TV/RTV	24.1	97.34	Alive	CD4 decrease Viral load increase
		Nevirapine	1	290	160	10913	472121	TL/A TV/RTV	31.15	99.39	Alive	CD4 decrease Viral load increase
		Zidovudine, Lamivudine, Nevirapine	1	112	161	50603	48887	TL/A TV/RTV	35.6	95.81	Alive	CD4 increase; Viral load decrease
		Zidovudine, Nevirapine	1	253	174	9008	248242	TL/A TV/RTV	53.9	95.95	Alive	CD4 decrease Viral load increase
13	Zidovudine, Lamivudine, Nevirapine, Stavudine, Tenofovir, Efavirenz	Zidovudine, Lamivudine, Stavudine, Nevirapine	1	240	436	30694	TND	No	61.13	99.7	Alive	CD4 increase Viral load decrease
14	Zidovudine, Lamivudine, Nevirapine, Tenofovir, Efavirenz	Zidovudine, Lamivudine, Nevirapine, Tenofovir, Efavirenz	1	312	193	12344	56094	No	47.1	98.11	Alive	CD4 decrease Viral load increase
			1	267	357	11847	TND	No	66.2	99.3	Alive	CD4 increase Viral load decrease
15	Zidovudine, Lamivudine, Nevirapine, Efavirenz	Lamivudine, Nevirapine, Efavirenz	1	265	272	151379	118265	TL/A TV/RTV	40.21	97.14	Alive	CD4 increase Viral load decrease

Table 1 (b) Drug resistance pattern of patients whose end point viral load was not available

Sr. No.	Drug Regimen	Drug resistance	No. of patients	CD4 count at DSA	End point CD4 count	Viral load at DSA	Second Line Regimen	Adherence (%)	Status of the patient	Remark
1	Stavudine, Lamivudine, Efavirenz, Nevirapine, Zidovudine	Lamivudine, Efavirenz, Nevirapine, Zidovudine	1	129	143	17082	No	96.52	Lost to follow up	CD4 Increased
2	Stavudine, Lamivudine, Efavirenz, Nevirapine, Tenofovir	Nevirapine, Efavirenz	1	58	98	373829	No	98.68	Dead	CD4 Increased
3	Stavudine, Lamivudine, Efavirenz, Zidovudine, Nevirapine, Tenofovir	Stavudine, Lamivudine, Efavirenz, Zidovudine, Nevirapine	1	87	175	34015	No	96.99	Dead	CD4 Increased
4	Stavudine, Lamivudine, Efavirenz, Zidovudine, Nevirapine	Stavudine, Zidovudine	1	258	79	206019	TL/ATV/RTV	99.45	Dead	CD4 Decreased
5	Stavudine, Lamivudine, Nevirapine, Efavirenz, Tenofovir, Zidovudine	Zidovudine, Lamivudine	1	134	295	4300	No	99.63	Alive	CD4 Increased
6	Stavudine, Lamivudine, Nevirapine, Zidovudine, Tenofovir, Efavirenz	Zidovudine, Tenofovir, Stavudine, Lamivudine, Nevirapine, Efavirenz	1	208	15	315003	No	98.47	Alive	CD4 Decreased
7	Tenofovir, Lamivudine, Efavirenz	Lamivudine, Efavirenz	1	265	140	140393	No	88	Dead	CD4 Decreased
		Lamivudine, Tenofovir, Efavirenz	1	435	133	162109	No	86.73	Alive	CD4 Decreased
			1	348	442	85743	No	96.68	Alive	CD4 Increased
		NONE	1	308	246	51301	No	86.99	Alive	CD4 Decreased
			1	385	307	175994	No	87.68	Dead	CD4 Decreased
			1	27	40	2095	No	89.7	Dead	CD4 Increased
8	Tenofovir, Lamivudine, Efavirenz, Nevirapine	Tenofovir, Lamivudine, Efavirenz, Nevirapine	1	194	143	54987	No	99.12	Alive	CD4 Decreased
		Zidovudine, Lamivudine, Tenofovir, Nevirapine, Efavirenz	1	37	91	25338	No	98.32	Alive	CD4 Increased
		Tenofovir	1	640	142	1058687	SL/ATV/RTV	89.66	Alive	CD4 Decreased
		NONE	1	168	234	103158	2L/ATV/RTV	93.27	Alive	CD4 Increased
		Lamivudine, Nevirapine, Efavirenz	1	264	37	203217	No	95.27	Dead	CD4 Decreased
		Lamivudine, Tenofovir, Efavirenz, Nevirapine	1	168	188	163223	No	92.22	Alive	CD4 Increased
		Nevirapine, Efavirenz	1	39	58	310718	No	91.59	Dead	CD4 Increased
		Lamivudine, Tenofovir, Efavirenz	1	231	254	1063	No	93.81	Alive	CD4 Increased
9	Zidovudine, Lamivudine, Efavirenz, Stavudine, Nevirapine, Tenofovir	Zidovudine, Lamivudine, Efavirenz, Stavudine, Nevirapine, Tenofovir	1	27	64	697164	No	99.24	Alive	CD4 Increased
		Zidovudine, Tenofovir, Stavudine, Efavirenz, Nevirapine	1	108	161	2290	No	95.61	Alive	CD4 Increased
10	Zidovudine, Lamivudine, Efavirenz, Nevirapine	Lamivudine, Efavirenz, Nevirapine	1	73	958	290151	No	98.89	Alive	CD4 Increased
11	Zidovudine, Lamivudine, Efavirenz, Nevirapine, Tenofovir	NONE	1	172	219	156652	TL/ATV/RTV	97.39	Alive	CD4 Increased
		Zidovudine, Lamivudine	1	222	510	159904	No	82.21	Alive	CD4 Increased
12	Zidovudine, Lamivudine, Nevirapine, Stavudine, Tenofovir, Efavirenz	Zidovudine, Lamivudine, Nevirapine, Stavudine, Tenofovir, Efavirenz	1	207	306	1997	No	97.23	Alive	CD4 Increased
13	Zidovudine, Lamivudine, Nevirapine, Tenofovir, Efavirenz	Zidovudine, Tenofovir, Nevirapine, Efavirenz	1	253	314	1195	No	95.56	Alive	CD4 Increased
		Lamivudine, Tenofovir, Efavirenz, Nevirapine	1	150	266	1694	No	98.51	Alive	CD4 Increased
14	Zidovudine, Lamivudine, Nevirapine, Tenofovir	Zidovudine, Lamivudine, Nevirapine, Tenofovir, Efavirenz	1	87	142	3698	No	99.25	Alive	CD4 Increased
15	Zidovudine, Lamivudine, Nevirapine, Tenofovir, Efavirenz	NONE	1	157	380	2991	RAL/LPV/RTV	97.97	Alive	CD4 Increased
		Zidovudine, Nevirapine, Efavirenz	1	255	362	1219	No	95.41	Alive	CD4 Increased
16	Zidovudine, Lamivudine, Nevirapine, Efavirenz, Tenofovir	Lamivudine, Efavirenz, Nevirapine	1	54	191	2950	No	97.09	Dead	CD4 Increased

Data of viral load at study end point was not available for 33 North Indian patients [Table 1 (b)]. It shows that although CD4 count improved in 24 North Indian patients, 5 of them died. Two North Indian patients on TLE regimen who died during treatment did not show resistance to any ART drug. 18 North Indian patients who were alive had improved CD4 count (11 patients had less than 300/mm³ and 7 patients had it \geq 300/mm³). Five North Indian patients were shifted on second-line regimen out of which one died

during the treatment. There was no significant difference between starting and end point median CD4 count ('p' value 0. 189) of these 33 North Indian patients.

Median duration between diagnosis and initiation of treatment was 8 weeks (Range: 1 to 460 weeks). Median duration of treatment was 41.5 months (range 10.3 to 86.6 months) and treatment adherence was 97.34% (range 82.21% to 99.7%).

Table 2: Drug resistance frequency analysis (multiple observations due to different regimens)

Sr. No.	Class of ART drug	Name of the drug	End point viral load available	End point viral load not available	Total
			Number out of 24 (%)	Number out of 33 (%)	
1	NNRTI	Nevirapine	18 (75)	19 (57.57)	37
2		Efavirenz	16 (66.67)	22 (66.66)	38
3	NRTI	Lamivudine	16 (66.67)	19 (57.57)	35
4		Zidovudine	10 (41.67)	13 (39.39)	23
5		Tenofovir	5 (20.83)	13 (39.39)	18
6		Stavudine	3 (12.5)	6 (18.18)	9
7		Abacavir	1 (4.16)	0 (0.0)	1

When drug resistance pattern of these patients was studied, Efavirenz and Nevirapine resistance was observed in most of the patients followed by Lamivudine and Zidovudine (Table 2). Few patients were resistant to tenofovir, stavudine and abacavir. Thus, resistance to NNRTIs was observed more frequently than NRTIs.

Discussion

Treatment failure can be assessed by an immunological, virological or clinical measure. The establishment of the measurement of RNA copies is a surrogate marker for HIV disease progression [11]. Low-level RNA copies may not predict virologic failure, however, the high RNA copy number is a risk of treatment failure [12] Successful antiretroviral treatment is specifically defined as viral suppression in people living with HIV (PLHIV) [13]. The viral load has become the cornerstone for evaluating the success of anti-retroviral therapy in clinical and research. Few North Indian patients in the present study had higher end point viral loads than baseline in presence of resistance to the first line ART drugs.

It has been suggested that, CD4 count of individual patients after therapy confirms the risk of the progression of AIDS or death [14] But in present study, decline in CD4 count was observed irrespective of drug resistance status of North Indian patients. Few North Indian patients died during treatment although their CD4 count was increased.

The clinical goal for each patient requires an effective, active, tolerable and minimal side effects regimen to achieve maximal clinical benefits to avoid the definition of treatment failure. In this study, drug resistance was found to various first line drugs such as zidovudine, lamivudine, tenofovir, stavudine, efavirenz and nevirapine. HIV drug resistance has been monitored by affordable HIV drug resistance testing in Sub-Saharan Africa [15] From the multi-centre study in India, it was concluded that Nevirapine therapy is reasonable alternative for efavirenz [16]. In this North Indian population study, resistance to Nevirapine and Efavirenz was most commonly observed.

Tenofovir is an important regimen included in the first line antiretroviral therapy. Tenofovir based virological monitoring predicted treatment failure for patients [17]. In this study, 18 North Indian patients were found to be resistant to Tenofovir [18] addressed the monitoring of the degree of genotypic resistance to zidovudine. In this study, Lamivudine resistance was found in 35 North Indian patients. Zidovudine resistance was found in 23 North Indian patients. Similar finding was observed in a study where in zidovudine and lamivudine combinatorial therapy, both zidovudine and lamivudine therapy failure were marked in HIV-1 infected North Indian patients [19].

Stavudine exhibits antiretroviral activity as a monotherapy or combination therapy to manage the adults with HIV infection [20] The rate of treatment failure for stavudine/lamivudine /nevirapine was determined in Asian region [21]. In this study, out of 11 North Indian patients on SLE/SLN combination therapy, 9 North Indian patients were developed resistance to stavudine.

Abacavir is a suitable antiretroviral drug with lamivudine for treatment of HIV patients [22] One North Indian patient was treated with ALN regimen and Abacavir treatment failure was observed in that one patient.

The management of HIV resistance differs in lower middle-income countries compared to high income countries. It has been recommended that HIV drug resistance testing should like a point of care test [23]. This study utilized WHO dried blood spot protocol 2010 polymerase chain reaction and sequencing primers. Thermal conditions are useful in genotyping test which can reduce the cost of the test.

In India, the antiretroviral therapy is still introduced at an advanced stage of disease without drug resistance testing. This is the main cause of mortality of HIV patients. The studies assessing the relationship between DRMs and their effect on treatment outcome are limited. An insight into HIV drug resistance pattern and its effect on prognosis of AIDS in individual patients is important. It can also enable the health care providers to monitor HIV drug resistance over the period of treatment. However, utility of such test at the level of national health program needs to be studied in detail before formulation of policy.

Conclusion

This is a secondary data analysis based on available records of a very few North Indian patients. The effect of drug resistance on CD4 count, viral suppression and clinical outcome could not be established.

To support evidence-based policy decision, determinants of HIV drug resistance and its effect on ART outcome need to be explored further in a structured manner in North Indian population. Introducing molecular drug resistance testing in the program in the presence of an appropriate evidence may lead to proper management of healthcare resources for HIVDR management in North Indian population. Implementation science research on a larger scale may assist in strategizing and prioritizing interventions for HIV drug resistance control. Monotherapy or combination therapy based on individualized genotypic testing in North Indian population may prove an effective intervention if planned on the basis of evidence generated through such research.

Abbreviations

HIV: Human Immunodeficiency Virus, AIDS: Acquired Immunodeficiency Syndrome, ART: Antiretroviral Therapy, NRTI: Nucleoside reverse transcriptase inhibitor, NNRTI: Nonnucleoside reverse transcriptase inhibitor, DR: Drug resistance.

Declarations

Ethics approval and Informed consent

The HIV drug resistance study was approved by the institutional ethics committee. The Institute ethics committee is representing as the guidelines of Indian Council of Medical Research [9]. The study was approved by the Institutional Review Board that is Institute Human Ethics Committee of National JALMA Institute for Leprosy and Other Mycobacterial Diseases, (Indian Council of Medical Research), Dr. M. Miyazaki Marg, Taj-ganj, Agra-282004. The registration number of institute Institute Human Ethics Committee was ECR/257/Inst/ UP/ 2013. The ethics committee meeting was held on 27.5.2016 at National JALMA Institute for Leprosy and Other Mycobacterial Diseases, Agra for the project entitled "Characterization of drug resistant HIV-1 mutants of Agra region, India by genomic and proteomic approaches". Renewal of registration of Institute Human Ethics Committee of National JALMA Institute for leprosy and Other Mycobacterial Diseases was done by Central Drugs Standard Control Organization (CDSCO) with registration no. ECR/257/Inst/UP/2013/RR-20 dated 19th June 2020 and provisional registration with department of Health Research, Ministry of Health and Family Welfare, Govt. of India, File number- EC/NEW/INST/2020/792 dated 27th July 2020.

The study protocol and informed consent was approved by Institute Human Ethics Committee of National JALMA Institute for Leprosy and Other Mycobacterial Diseases, (Indian Council of Medical Research), Dr. M. Miyazaki Marg, Taj-ganj, Agra-282004. The informed consent of each study patient was taken by the information leaflet.

Consent for publication

Not applicable

Availability of Data and Materials

Not required

Competing interests

All authors declared no conflict of interest.

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Author's contribution

SKB: Manuscript write up and data collection, data analysis, AKB: Concept design for secondary data analysis, AY: Statistical Analysis of this paper and manuscript write up, SPT: Method design of the study, TPS: Patient study, SJ: Review the paper, SAP: Review the paper, KKM: Review the paper, concept design and manuscript write up.

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