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Risk of hepatitis B virus reactivation during immunosuppressive treatment

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Abstract. – OBJECTIVE: In this study, we aimed to rate Hepatitis B Virus (HBV) reactivation, risk factors for reactivation and compare the efficacy of prophylactic antiviral therapy in patients who initiated immunosuppressive therapy.

PATIENTS AND METHODS: A total of 177 patients with Chronic Hepatitis B or resolved HBV infection who had received immunosuppressive treatment were analyzed in this retrospective study. Demographic features, relevant liver tests, prophylactic treatment type, duration of treatment, transaminase levels and HBV serology and clinical conditions were recorded from all patients who received prophylactic treatment.

RESULTS: Eleven reactivation occurred in all groups. The mean age of patients who developed reactivation was statistically significantly lower (p=0.049). Three (27.3%) of the patients were male and 8 (72.7%) were female (p=0.66). Eight (36.36%) of 22 HB surface antigen (HBsAg) positive patients developed reactivation, 3 (155%) of 155 HBsAg negative patients developed reactivation. HBsAg positivity was determined as a risk factor for reactivation (p<0.001). There was no significant difference neither in reactivation, nor in the type of antiviral treatment (p=0.2) according to anti-HBs serology (p=0.366).

CONCLUSIONS: As a result, early age, baseline HBsAg positivity, moderate risk group, baseline HBV DNA positivity were associated with reactivation. Gender, immunosuppressive therapy type, preemptive antiviral therapy type, and anti-HBs titers were not associated with reactivation.

Key Words:
Immunosuppressive treatment, HBV reactivation, Entecavir, Tenofovir.

Introduction

Hepatitis B virus (HBV), a double-stranded DNA virus, is a member of the *hepadnaviridae* family, and the consequences of HBV infection, such as acute hepatitis, fulminant hepatitis, chronic hepatitis, liver cirrhosis, and hepatocellular carcinoma, are important public health concerns[1]. A variety of vaccines and antiviral drugs have been developed to prevent and treat infections caused by the hepatitis B virus, with the primary therapeutic target of antiviral drugs being to eliminate the HBV surface antigen (HBsAg). The ultimate success of antiviral treatment is not possible without ensuring an absolute removal of the covalently closed circular DNA (cccDNA) from the hepatocyte nucleus; unfortunately, no treatment is currently available to achieve this. Consequently, patients with a history of contact with HBV, including those who may have developed natural immunity or are HBsAg positive but are not indicated for antiviral therapy, continue to be at risk of HBV reactivation and acute exacerbation when receiving immunosuppressive therapy.

In this study, we aimed to define the risk and rate of HBV reactivation in patients who had initiated immunosuppressive therapy and to compare the efficacy of tenofovir (TDF) and entecavir (ETV) in these patients.

Patients and Methods

We scanned the hospital's medical database (Enlil, v.2.20.14 20200406) for patients who had visited our hospital's gastroenterology outpatient clinic between January 2016 and December 2018. Patients testing positive for HBsAg and/or Hepatitis B core antigen antibody of IgG type (anti-HBcIgG), who were planned to receive immunosuppressive therapy and addressed to the outpatient clinic for prophylactic treatment (n=425) were considered for inclusion in the study. Of these, those who had completed at least one cycle of immunosuppressive therapy and had started prophylactic treatment (tenofovir or entecavir) were included in the study. Patients

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aged below 18 years of age, those receiving concurrent prophylactic or therapeutic antiviral therapy for chronic hepatitis B (CHB) infection, those having chronic liver disease due to another etiology (non-alcoholic fatty liver disease was not excluded), were excluded from the study.

The following data were recorded for all patients: demographic characteristics, relevant laboratory test results [such as liver function tests, Enzyme-Linked ImmunoSorbent Assay (ELISA), etc.], details of the immunosuppressive treatment planned for the patient, the phase of CHB, the risk group allotted, whether the patient received prophylactic treatment and the duration (if receiving), transaminase levels during treatment, serum HBV-DNA levels, and other clinical conditions.

The 425 patients were evaluated for CHB and divided into three risk groups based on the serological evaluation and immunosuppressive therapy to be received. Low risk group was defined as lower than 1% for reactivation HBV, medium risk group was 1-10%, and high-risk group was 10-20%.

In the majority of the patients, ETV and TDF treatments were used as prophylactic antiviral therapy, so the patients were divided into two groups according to the two treatments. The patients' clinical variables (symptoms due to liver disease, general condition, new symptoms) and laboratory variables (deterioration in liver function tests or an increase in HBV-DNA positivity) were recorded from the beginning of the treatment. Additionally, complications during treatment and reactivation rates were compared.

CHB reactivation was defined as: a) the occurrence of detectable HBV-DNA levels in patients with previously negative baseline HBV-DNA following immunosuppressive therapy; b) an increase of > 2 $\log_{10}$ IU/ml in the patient's HBV-DNA levels (in literature, this is defined as a 10-fold increase compared to the basal HBV-DNA levels), in patients with initial HBV-DNA positivity; and c) reverse seroconversion (HBsAg-positive when HBsAg negative/anti-HBc positive) were used for detecting reactivation. Clinical data regarding follow-ups and prognoses with reactivation development were recorded.

Statistical Analysis

The Statistical Package for the Social Sciences Version 22.0 (IBM Corp., Armonk, NY, USA) program was used for statistical analysis. Patients with missing data were excluded. Binary variables of those with or without reactivation and those receiving Tenofovir and Entecavir were compared separately by the Fisher's exact test. Kolmogorov-Smirnov test was checked to determine whether it was in normal distribution. Independent variables between groups were compared with Student's *t*-test. For all tests, $p<0.05$ was considered significant.

Results

The data of 425 patients who initiated immunosuppressive therapy in our hospital's gastroenterology outpatient clinic and were referred for prophylactic antiviral therapy were scanned. One hundred seventy-seven patients who completed at least 1 cycle of immunosuppressive therapy and started prophylactic therapy were included in this study. The study flow chart is shown in Figure 1.

The demographics and clinical characteristics of the study population together with the laboratory findings about hepatitis B are presented in Table I.

Monoclonal antibodies, anthracyclines, antimetabolites, vinca alkaloids, anti-tumor antibiotics, cytokine and integrin inhibitors, tyrosine kinase inhibitors and systemic steroids were planned as immunosuppressive neoplastic drug therapy in all patients.

The treatment was discontinued due to the completion of the prophylactic treatment period after the immunosuppressive treatment in only 9 (5.1%) patients. While no reactivation finding was detected in 166 (93.8%) patients, with the results obtained, reactivation has been developed in 11 (6.2%) patients (Table I).

The mean age of all study group was 61.12±10.99 years. The youngest was 27 and the oldest was 84. The average duration of antiviral therapy use was 19.73 months.

The demographical and clinical data of the patients according to risk groups were presented in Table II.

In patients treated with ETV, older male sex was more common, were in more low-risk groups, and were receiving more systemic chemotherapy than the other groups. Detailed demographics, clinical characteristics, and laboratory data regarding to type of prophylactic treatment were presented in Table III.

One hundred twenty-four (70.01%) of the patients received immunosuppressive therapy due to solid tumors, 48 (27.1%) of them due to rheumatological diseases, 3 (1.7%) of them due to dermatological autoimmune diseases and 2 (1.1%) of them due to hematological malignancy. There

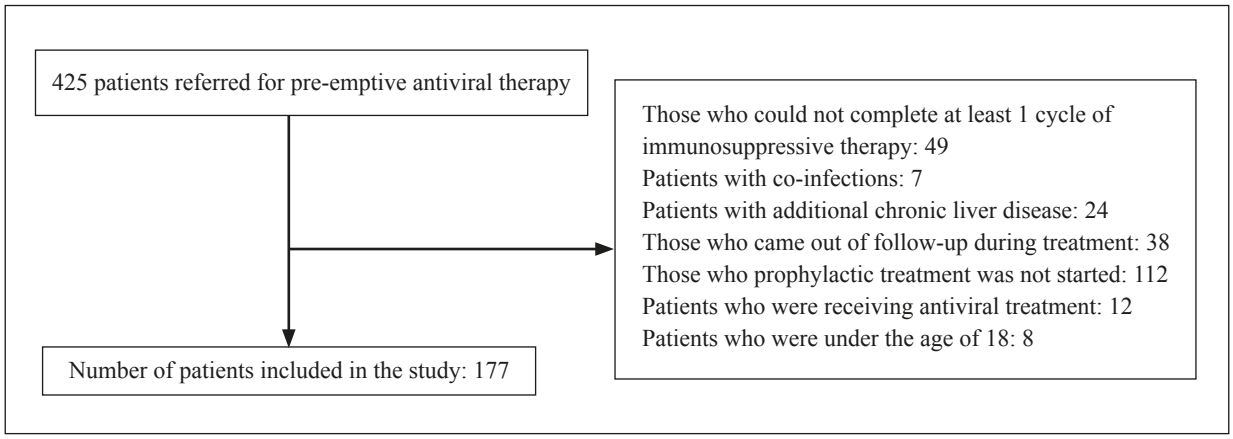

Figure 1. Study flow chart.

was no statistically significant difference between the prophylactic treatment groups-based distribution of the systemic diseases which caused the patients included in the study to receive immunosuppressive therapy (p=0.105).

Of the patients who received systemic chemotherapy, 89 (71.8%) received ETV and 34 (27.4%) TDF. In 1 (0.8%) patient who received systemic chemotherapy, lamivudine (LAM) was switched to ETV due to drug resistance, and then to TDF due to reactivation. Of the patients using monoclonal antibodies, 26 (49.1%) received ETV, and 25 (47.2%) TDF. For 1 (1.9%) patient in this group, TDF was switched to ETV due to side effects and for another 1 (1.9%) patient, from LAM to ETV due to drug resistance. There was a statistically significant difference between the distribution of patients included in the study to prophylactic treatment groups according to the types of immunosuppressive therapy (p=0.011). This difference was due to the higher use of ETV among patients receiving systemic chemotherapy.

The mean age of the patients with reactivation development was 54.82/year, it was 61.54/year for those without reactivation. The mean age of the patients with reactivation development was statistically significantly lower (p=0.049). Three (27.3%) of the patients with reactivation development were male and 8 (72.7%) were female. Although, there was no statistically significant difference between genders in terms of reactivation development (p=0.066).

The reactivation was developed in 8 (36.36%) of the 22 HBsAg positive patients, in 3 (1.94%) of the 155 HBsAg negative patients. Positive serology for HBsAg had a higher risk for reactivation development at a statistically significant level (p<0.001).

The number of patients who received systemic chemotherapy was 8 (72.7%), whereas those who used monoclonal antibody were 3 (27.3%). There was no statistically significant difference between immunosuppressive therapy types in terms of reactivation development (p=0.735). Reactivation development was observed in 1 (9.1%) patient in the low-risk group, 9 (81.8%) in the medium risk group, and 1 (9.1%) in the high-risk group. There was a statistically significant difference between the risk groups in terms of reactivation development (p=0.003).

Five (45.5%) patients received ETV, 4 (36.4%) patients TDF, and 2 (18.2%) patients LAM at the beginning of the prophylactic treatment. There was no significant difference in terms of initial prophylactic treatment types in terms of reactivation development (p=0.2). When the basal anti-HBs of the patients with reactivation development was evaluated, 7 (63.6%) had negative serology and 4 (36.4%) had positive serology. There was no statistically significant difference between the groups (p=0.366). Seven of the patients who developed reactivation had positive initial HBV-DNA serology and 4 of them negative. The positive HBV-DNA at the beginning of the treatment indicated a high risk of reactivation development (p<0.001). The clinical characteristics of 11 patients with reactivation development are shown in Table IV.

Discussion

Despite the availability of prophylactic as well as therapeutic antiviral therapies, as the cccDNA continues to dwell in the hepatocyte

Table I. The demographics and clinical characteristics of the study population (n=177).

		n	%
Gender	Male	94	53.1
	Female	83	46.9
Active ingredient	Entecavir	115	65.0
	Tenofovir	59	33.3
	ETV - TDF (switch)	1	0.6
	LAM - ETV (switch)	1	0.6
	LAM - ETV - TDF (switch)	1	0.6
Risk Group	Low (<1%)	99	55.9
	Medium (1-10%)	76	42.9
	High (10-20%)	2	1.1
Drug withdrawal	Not Present	168	94.9
	Present	9	5.1
Side effect	Not Present	176	99.4
	Present	1	0.6
Discontinuation of drug	Not Present	137	77.4
	Present	40	22.6
Re-activation	Not Present	166	93.8
	Present	11	6.2
HBsAg*	Negative	155	87.6
	Positive	22	12.4
	Unknown	-	-
Anti HBs*	Negative	28	15.8
	Positive	132	74.6
	Unknown	17	9.6
Anti HBcIgG*	Negative	0	0.0
	Positive	169	95.5
	Unknown	8	4.5
HBV-DNA*	Negative	55	31.0
	Positive	22	12.4
	Unknown	100	56.4

TDF, Tenofovir; ETV, Entecavir; LAM, Lamivudine; HBsAg, Hepatitis B surface antigen; Anti HBs, Hepatitis B surface antigen antibody; Anti-HBcIgG, Hepatitis B core antigen antibody of IgG type; HBV-DNA, Hepatitis B Virus deoxy-ribonucleic acid. *level at the start of the study.

nucleus, serving as a seed for HBV, the virus may be reactivated and start replicating under appropriate conditions, such as immunosuppression. Therefore, patients with a history of HBV contact are always at risk for HBV reactivation and acute exacerbation. Thus, current clinical guidelines[2-5] recommend that all patients who are planned to receive immunosuppressive therapy should be screened for serological evidence of previous HBV infection and undergo prophylactic treatment, if necessary.

International guidelines[2-4] have described certain indications for antiviral prophylaxis for

Table II. The demographical and laboratory data of patients according to risk groups.

Risk Groups	n	Age (y)	Sex		HBsAg		Anti-HBcIgG	
			Male n(%)	Female n(%)	Negative n(%)	Positive n(%)	Positive n(%)	Unknown n(%)
Low (<1%)	99	64.4 ± 9.7	60 (63.8)	39 (47)	99 (63.9)	0 (0)	99 (58.6)	0 (0)
Medium (1-10%)	76	56.8 ± 11.2	34 (36.2)	42 (50.6)	55 (35.5)	21 (95.5)	69 (40.8)	7 (87.5)
High (10-20%)	2	61.5 ± 6.3	0 (0)	2 (2.4)	1 (0.6)	1 (4,5)	1 (0.6)	1 (12.5)
		p* < 0.001	***p* = 0.021***		***p* < 0.001***		***p* < 0.001***	

y, years; HBsAg: Hepatitis B surface antigen; Anti-HBcIgG: Hepatitis B core antigen antibody of IgG type. *: There is a statistically significant difference.

Table III. The demographical, clinical characteristics and laboratory data of patients according to risk groups.

		n	Treatment groups					p
			ETV	TDF (switch)	TDF - ETV (switch)	LAM - ETV (switch)	LAM -ETV (switch)	
Age (y)		177	62.9 ± 10.6	57.6 ± 10.6	75.00	41.00	59.00	0.002*
Gender n (%)	Male	94	68 (73.3)	25 (26.6)	0 (0)	0 (0)	1 (1.1)	0.036*
	Female	83	47 (56.6)	34 (41.0)	1 (1.2)	1 (1.2)	0 (0)	
HBV-DNA at the	Negative	54	33 (61)	20 (37)	1 (1.9)	0 (0)	0 (0)	0.644
beginning n (%)	Positive	20	10 (50)	9 (45)	0 (0)	1 (5)	0 (0)	
Immunosuppressive	SC	124	89 (71.8)	34 (27.4)	0 (0)	0 (0)	1 (0.8)	0.011*
treatment type n (%)	MA	53	26 (49.1)	25 (47.2)	1 (1.9)	1 (1.9)	0 (0)	
Risk Groups n (%)	Low (<1%)	99	75 (75.8)	24 (24.2)	0 (0)	0 (0)	0 (0)	0.036*
	Medium (1-10%)	76	39 (51.3)	34 (44.7)	1 (1.3)	1 (1.3)	1 (1.3)	
	High (10-20%)	2	1 (50.0)	1 (50.0)	0 (0)	0 (0)	0 (0)	

ETV, Entecavir; TDF, Tenofovir; LAM, Lamivudine; y, years; HBV DNA, Hepatitis B Virus deoxy-ribonucleic acid; SC, Systemic chemotherapy; MA, Monoclonal antibody. *: There is a statistically significant difference.

HBsAg-positive patients; however, there is no consensus regarding the management of HBsAg-negative and anti-HBc-positive patients undergoing immunosuppressive therapy. Furthermore, complete and definite risk classification is not possible in all patients; therefore, real-life data are still required to predict which patients may develop CHB reactivation.

This study aimed to determine the reactivation rates and risk factors (such as age, sex, and biochemical parameters) that may affect the development of reactivation in patients receiving immunosuppressive therapy concurrently with prophylactic treatment. Out of the 425 patients scanned, 177 patients were included in the study; of these, 11 patients (8 females, 3 males) (6%) had

Table IV. Clinical characteristics of 11 patients with reactivation development.

Patient number	Age (y)	Gender	Basal anti-HBs	Basal HBV-DNA	Basal HBsAg	Basal anti-HBcIgG	Immunosuppressive therapy	Duration of treatment (months)	Pre-emptive therapy	Reactivation criterion	Time until reactivation (months)	Risk Group
1	41	F	-	+	+	+	MA	71	LAM-ETV	HBV-DNA+	20	Med
2	66	F	+	-	-	+	MA	6	TDF	HBV-DNA+	8	Med
3	59	M	-	+	+	+	SC	67	LAM-ETV-TDF	HBV-DNA+	47	Med
4	57	F	-	+	+	+	MA	36	ETV	HBV-DNA+	19	High
5	68	F	-	-	+	+	SC	38	ETV	HBV-DNA+	8	Med
6	43	F	+	+	+	+	SC	21	TDF	HBV-DNA+	14	Med
7	48	F	-	+	+	+	SC	23	ETV	HBV-DNA+	16	Med
8	63	M	-	+	-	+	SC	26	TDF	HBV-DNA+	9	Med
9	40	F	+	-	+	+	SC	30	ETV	HBsAg+	27	Med
10	61	F	+	-	-	+	SC	6	TDF	HBV-DNA+	16	Low
11	56	M	-	+	+	+	SC	21	ETV	HBV-DNA+	12	Med

Y, years; Anti HBs, Hepatitis B surface antigen antibody; HBV DNA, Hepatitis B Virus deoxy-ribonucleic acid; HBsAg, Hepatitis B surface antigen; Anti-HBcIgG, Hepatitis B core antigen antibody of IgG type; F, Female; M, Male; SC, Systemic chemotherapy; MA, Monoclonal antibody; NA, Not Applicable; TDF, Tenofovir; ETV, Entecavir; LAM, Lamivudine; Med, medium.

developed CHB reactivation. Despite a greater number of female patients developing viral reactivation compared to male patients, this difference was not statistically significant (p=0.066). Cho et al[6] and Perez-Alvarez et al[7] observed concurring findings in their studies; on the other hand, other studies[8-10] that included almost 13,000 patients described the male sex as a risk factor for reactivation.

In this study, the mean age of patients undergoing reactivation was 54.82±12.2 years, which was significantly lower than those who did not undergo CHB reactivation (61.54±6 years) (p<0.001). So far, there is no evidence in the literature corroborating the role of young age as a risk factor for viral reactivation. On the contrary, Seto et al[11] found that patients with HBV reactivation were over 50 years of age. Likewise, Kusumoto et al[12,13] found that increasing age was a risk factor for reactivation in two separate studies; they attributed the reason for more reactivation at older age to the fact that younger patients tended to be immunized with recently developed anti-HBV vaccines, whereas older patients were more likely to be immunized by encountering the virus itself. In Turkey, routine HBV vaccination has been carried out for the past 26 years, and there were no patients under 26 years of age among those included in our study; therefore, while vaccination status might have been a confounding factor for Kusumoto et al[12,13], it cannot be for ours. In two different case series[14-16] conducted in China, where HBV infection is considered an endemic disease, being over the age of 40 years[14,15] to 60 years[16] was reported as a risk factor for reactivation. Contrarily, four others[6,7,17,18], with a combined study sample of 1,881 patients, did not classify age as a risk factor for reactivation. Therefore, further research is warranted on this aspect.

In our study, in line with the literature, at the beginning of prophylactic treatment, eight patients were HBsAg-positive and three were HBsAg-negative; as anticipated, the reactivation risk in HBsAg-positive patients was significantly higher (p<0.001)[18-21]. Furthermore, the type of initial prophylactic treatment received did not affect the chances of reactivation development (p=0.2). Su et al[17] also reported that only a small number of patients (n=7/1,000) developed HBV reactivation in their study, and there was not statistically significant difference between groups in terms of prophylactic antiviral treatment types (p=0.21). Furthermore, Zhou et al[18] performed a statistical comparison of three antiviral molecules (lamivudine, ETV, and Telbivudine) used as prophylactic antiviral therapy and found that telbivudine users had a significantly higher risk of reactivation (p=0.014). Consequently, telbivudine use has been discontinued in many countries because of its side effects and low effect profile compared to other potent antivirals (e.g., ETV, tumor necrosis factor (TNF)].

The role of examining anti-HBsAg in CHB patients to determine possible candidates for immunosuppressive therapy has been debatable[22]. According to our results, the initial anti-HBs titres did not lead to a significant difference in terms of reactivation (p=0.366). Multiple studies[4,10,23-25] involving thousands of patients have shown that anti-HBs titres have a protective effect in CHB patients at risk of developing viral reactivation; this protective effect of positive anti-HBs titres can be attributed to the preventive effect of HBsAg reverse seroconversion. Therefore, the decision to initiate antiviral prophylaxis in anti-HBc-positive patients cannot be taken based solely on anti-HBs titres or its presence[4]. Current guidelines[26] for the management of CHB reactivation also report that there are insufficient data regarding the use of anti-HBs titres for prophylaxis recommendation.

Concurring with previous studies[12,18,23], we found that HBV positivity was a risk factor for reactivation. Moreover, when baseline alanine aminotransferase (ALT) values were considered, there was no significant difference between patients with and without reactivation (p=0.934). Other studies[6,11,17,18,23,27] conducted in geographical regions with a high prevalence of HBV have also reported that high ALT levels did not predispose the patient to a risk of reactivation.

Lastly, no statistically significant difference was observed in our study between the use of systemic chemotherapy and monoclonal antibody in terms of viral reactivation (p=0.735). Yazaki et al[28] and Su et al[17] found that patients receiving targeted therapy and using anti-CD20 agents have a significantly higher risk of reactivation. Considering these data, it can be reasonably assumed that anti-CD20 agents increase the risk of HBV reactivation by inducing a loss of CD (+) antigen-presenting cells that strengthen the T-lymphocyte response against HBV. In our study, the number of patients who received anti-CD20 agent treatment was very small.

Limitations

Our study has certain limitations. First, due to its retrospective nature, some parameters did not

have complete data entries at the beginning or during the follow-up; nevertheless, missing data did not affect the purpose or statistical evaluation of the study. Furthermore, our study was based on data from a single medical center; multicenter studies including large study samples are needed to support our findings.

Conclusions

In recent years, the widespread use of biologic and immunosuppressive drugs has led to a significant increase in HBV reactivation; thus, HBV screening should be done carefully at the beginning of immunosuppressive therapy to address the possible complications from reactivation. Prophylactic treatment with nucleoside analogues has significantly reduced the incidence, morbidity, and mortality of HBV reactivation. Nevertheless, risk assessment should be performed meticulously, and treatments should be planned based on the patient's immunosuppressive therapy and serology status.

In our study, factors that may have an effect on HBV reactivation were evaluated. We found that early age, initial HBsAg positivity, being in the intermediate risk group, and initial HBV-DNA positivity were associated with HBV reactivation. On the other hand, sex, type of immunosuppressive and prophylactic antiviral therapy used, and anti-HBs titres were not associated with reactivation. Despite the increasing incidence of HBV reactivation, the screening rates before immunosuppressive treatment and the awareness among physicians on this issue are insufficient to deal with the situation. In addition, there is a lack of strong evidence-based clinical data for the use of specific markers to predict or screen for reactivation. The risk factors affecting HBV reactivation identified in our retrospective analysis must be confirmed via prospective clinical trials before being implemented in clinical guidelines and treatment decisions.

Ethics Approval

The study complied with the principles outlined in the Declaration of Helsinki, and the Clinical Research Ethics Committee of the Faculty of Medicine, Tokat Gaziosmanpasa University approved the study protocol (19-KAEK-046).

Informed Consent

Informed consent was not required due to the retrospective nature of the study.

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Authors' Contributions

A.K., and S.T. were involved in planning and supervised the work. A.K. and S.T. processed the data, performed the analysis, drafted the manuscript and designed the figure. A.K. and U.S.C. aided in interpreting the results and worked on the manuscript. All authors read and approved the final version of the manuscript.

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Availability of Data and Materials

The data supporting this article are available from the corresponding author on reasonable request.

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