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Original Article

Evaluation of long-term efficacy of Imatinib in chronic phase CML patients in a tertiary care hospital of Eastern India

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ABSTRACT

Imatinib mesylate (IM) is the first innovative molecule which emerged as a definitive therapy targeting bcr-abl gene of Philadelphia chromosome +ve chronic myeloid leukemia (CML). The use of this drug has carved a path for disease-free life. Though newer congeners have already arrived, the use of IM is still highest among the tyrosine kinase inhibitors (TKIs) in countries like India. This prospective, analytical study was carried out on the patients of CML in chronic phase at the department of haematology of S.C.B medical college and hospital with a study follow-up for two years. Data regarding bcr-abl protein breakpoint and progression of disease were recorded. Kaplan-Meier curve with Log rank test was used for time-to-event analysis. The overall progression-free survival (PFS) was 85.4% and the cumulative hazard of achieving major molecular remission (MMR) was 1.5. 94.1% of patients were having p210 break-point but 50% of the p190 breakpoint patients had disease progression. Though cases of resistance to IM have emerged and are a matter of concern, the efficacy profile is still quiet beneficial in Indian patients.

KEYWORDS: imatinib mesylate, CML, breakpoint, PFS, MMR.

INTRODUCTION

Chronic Myeloid Leukemia (CML) is one of the commonest hematological malignancies seen in adult Indians [1]. WHO has designated fusion of ABL-BCR genes of chromosomes 9 & 22 as the characteristic of Philadelphia (Ph-) chromosome-positive CML. The management of patients with chronic myeloid leukemia (CML) has drastically changed following the introduction of different tyrosine kinase inhibitors (TKIs). Imatinib has been available in India and has been made accessible to all segments of the population because of patient assistance programs and cheaper generic versions. Even though there are improvements in survival, there are peculiar challenges in the Indian scenario [2, 3]. The second generation TKIs though more effective, are not affordable to the majority of population. The primary obstacle in improving the prognosis of patients with Ph-positive CML is drug resistance produced due to mutations resulting in disease progression [4-6]. Evaluation of molecular response of Imatinib therapy by monitoring bcr-abl protein helps in early diagnosis and detection of disease progression, which is relatively a new practice in eastern India. Thus the present study aims to study the long-term efficacy of Imatinib by monitoring the bcr-abl level in CML patients in chronic phase.

MATERIALS AND METHODS

This prospective open level observational study was carried out in CML-diagnosed patients attending both OPD and indoor of Clinical Haematology Department of SCB medical College & hospital, Cuttack and Acharya Harihara regional Cancer research institute, Cuttack. The study was conducted from November 2007 to May 2014. The study procedure is demonstrated in Figure 1.

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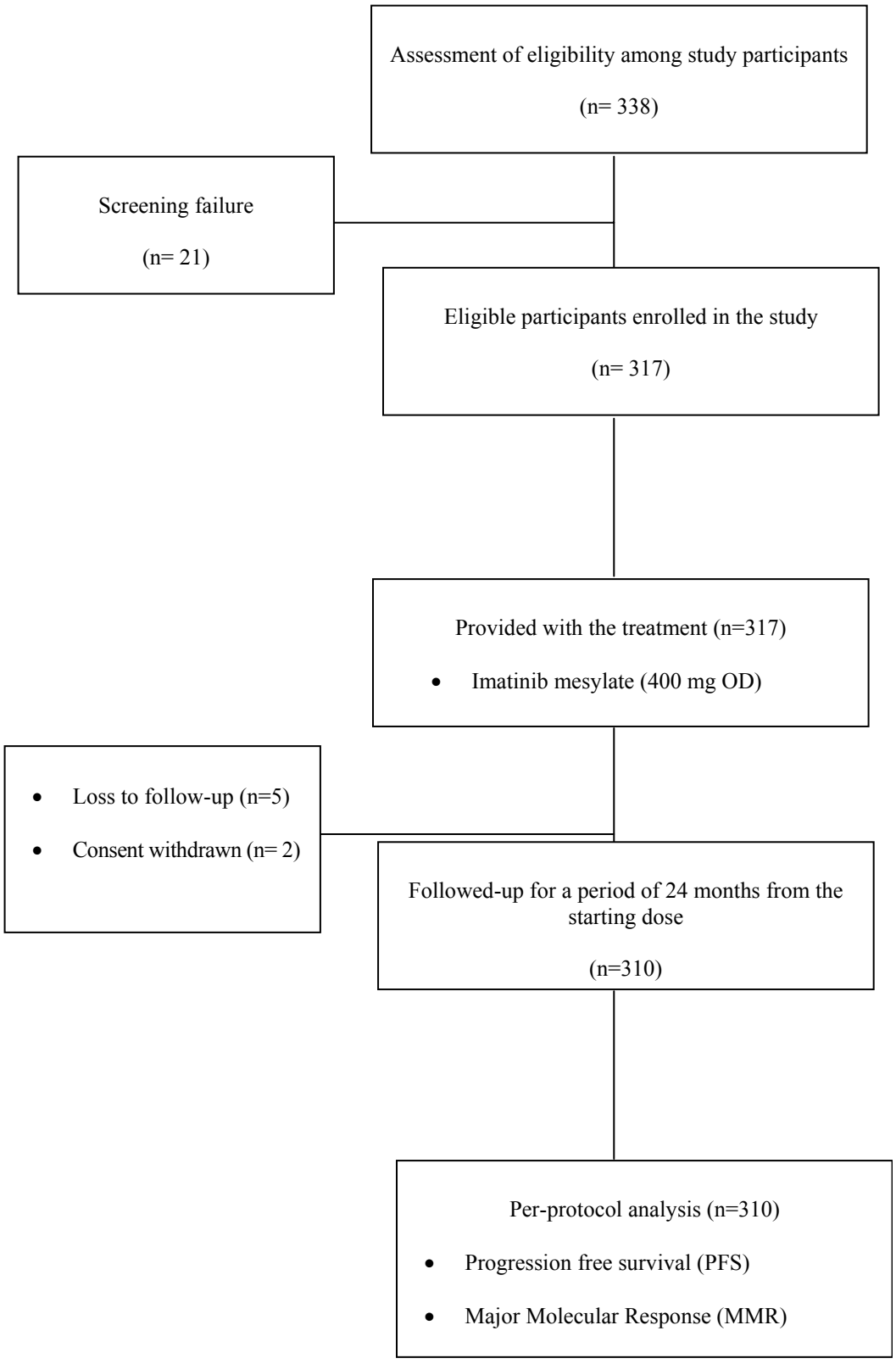

Figure 1. Study flowchart.

Inclusion criteria

Newly diagnosed adult patients (aged ≥ 18 years) of CML in chronic phase (CML-CP) were eligible for enrolment. The diagnosis was made by noting bcr-abl positivity through reverse transcription polymerase chain reaction (RT-PCR) test from bone marrow aspiration. Patients were considered as new if the diagnosis is made for the first time and has not received any treatment related to CML.

The chronic phase CML was defined as the presence of less than 10% blast cells in blood and bone marrow [7].

Exclusion criteria

- CML in either accelerated phase/blast crises.
- Known impairments in cardiac function including left ventricular ejection fraction < 45%, complete left bundle branch block, right bundle branch block plus left anterior hemi-block/bi-fascicular block, ventricular-paced pacemaker, congenital long QT syndrome, history or presence of clinically significant ventricular or atrial tachyarrhythmia, clinically significant resting bradycardia, QTcF>450 ms, myocardial infarction within the past 12 months, or other clinically significant heart disease.
- History of acute or chronic pancreatitis, impaired gastrointestinal function, concurrent uncontrolled medical conditions that would present unacceptable safety risks or compromise compliance with the protocol.
- Major surgery within the past 2 weeks or not recovered from the side effects of surgery.

Study design and treatments

Baseline patient characteristics including age, gender, spleen size, total leucocyte count, platelet count, percentage of myeloblasts, basophils, and eosinophils in peripheral blood were recorded. Bone marrow examination was done in all the cases at the time of diagnosis for the proper staging of the disease. The diagnosis of CML was confirmed by quantification of BCR-ABL by RT-PCR as per international scale and Sokal score was calculated.

Sokal score = Exp [0.0116 × (age in years - 43.4) + 0.0345 × (spleen size - 7.51) + 0.188 9 ([platelet count ⁄ 700]^2 - 0.563) + 0.0887 × (blast cell counts - 2.10)], where Exp is the exponential function[8].

All enrolled patients were treated with Imatinib at a starting dose of 400 mg once daily, for up to 24 months. Dose escalation was not allowed.

Assessments

Progression-free survival (PFS) was defined as the time from the first dose of study treatment until documented disease progression or death due to any cause. Molecular responses were assessed at 3, 12 and 24 months during study treatment using real-time quantitative PCR (RT-PCR) at a NABL and CAP accredited laboratory. Real-time quantitative PCR was performed on peripheral blood to look for molecular response, specifically major molecular response (MMR), which is defined as the reduction in the level of BCR-ABL to <0.1% in blood or bone marrow on the International scale [9].

All Imatinib-resistant patients were analysed in accordance to the protocol described by Branford and Hughes using an automated ABI377 sequencer (Applied Biosystems). HL60 cell line (ATCC # CCL-240TM) was used as a negative control and KCL22 cell line (DSMZ # ACC519) was used as a positive control. Sequences were analysed using Sequence Analysis Software V3.3 and Sequence Navigator Software V1.0.1 (Applied Biosystems). To confirm the mutation, opposite strand of the PCR product was sequenced. The whole procedure of RNA extraction, RT-PCR and sequencing was repeated again to confirm the findings.

Ethics

The study protocol was approved by the institutional ethics committee of SCB Medical College, Cuttack. Eligible patients were included only after obtaining written consent.

Statistical analyses

The statistical analysis was performed using SPSS (version 20.0). Survival curves were estimated according to the method of Kaplan and Meier, and statistical differences between curves were assessed by the log-rank test. Progression-free survival (PFS) is defined as the time during or after the treatment the patient remains free from loss of molecular and hematological response, progression to AP/blast phase or death. All response rates were calculated as raw proportions.

RESULTS

In this study, we analysed the data of 310 patients in chronic phase of CML who had been in line of study criteria and were followed-up for a period of 2 years. Within this study period we did not register any death. The baseline parameters are shown in Table 1.

Kaplan-Meier analysis was used to assess the progression-free survival (PFS), which estimated a 2-year PFS of 85.4% for the Imatinib-treated cases of CML-CP (Figure 2).

Break point analysis of our patients revealed that maximum belong to major breakpoint (p210), but disease progression occurred frequently in minor breakpoint (p190) (Table 2).

24 out of 45 (53.3%) cases were found to have kinase domain mutation. The different types of mutation detected in our study are depicted in Table 3.

When PFS was further analysed according to the severity of Sokal score, for low, intermediate and

Table 1. Baseline criteria.

Median age in year (Range)	**58 (18-74)**
Male **Female**	239 (77%) 71 (23%)
Median time since diagnosis (Range)	8 months (1-18 months)
Sokal Score **Low** **Intermediate** **High**	 43 (14%) 75 (24%) 192 (62%)
Mean Haemoglobin (gm/dl)	8.85 ± 0.35
Mean TLC ($x10^9$/L)	144.8 ± 10.6
Mean Platelet count ($x10^9$/L)	4.25 ± 6.35

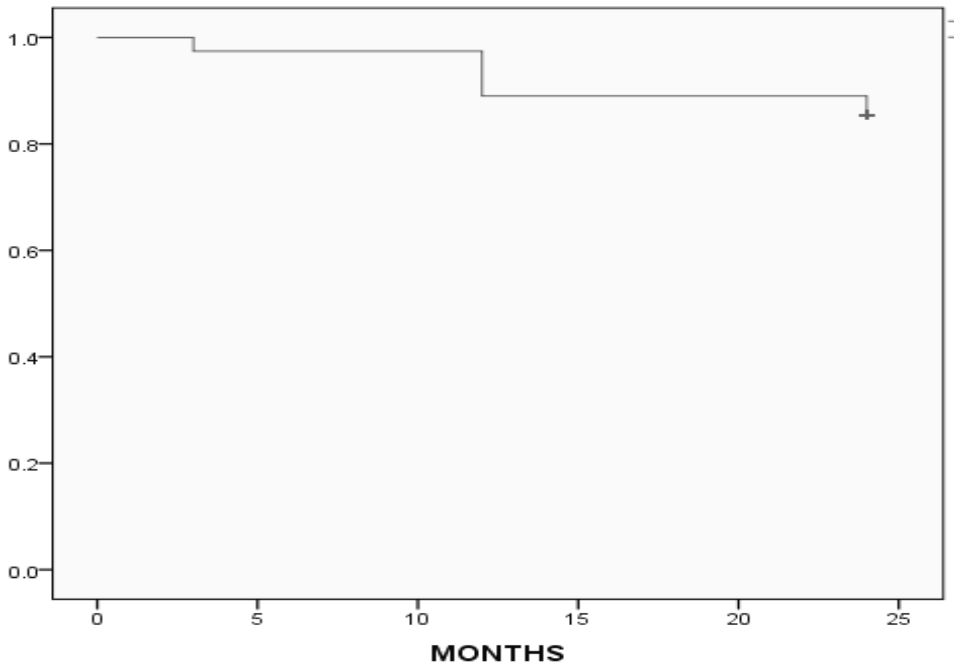

Figure 2. Progression-free survival (PFS).

Table 2. Break point analysis.

Break point	Number of patient (%)	Cases progressed to AP/BP (%)
Major (p210)	292 (94.1%)	36 (12.3%)
Minor (p190)	18 (5.9%)	9 (50%)

Table 3. Mutation analysis.

Mutation at Kinase domain	Number of cases (%)
F359C	7 (29%)
E255V	5 (21%)
T315I	4 (17%)
L387M	4 (17%)
V379I	3 (13%)
E255K	1 (3%)

high groups, it was 93%, 85.3% and 83.8%, respectively without any significant difference in between (p = 0.3) (Figure 3).

When achievement of MMR was assessed according to the severity of Sokal score, for mild, moderate and severe groups, it was 90%, 88.2% and 64.9%, respectively ($p < 0.05$) (Figure 4).

DISCUSSION

Imatinib mesylate, the revolutionary tyrosine kinase inhibitor, has changed the landscape of CML management and outcome in the last 20 years. This first intracellular targeted molecule selectively targets the oncogene and mostly spares the normal cells and thus possesses minimum adverse drug reaction. IRIS trial comparing the benefit of Imatinib with interferon led to the approval of this drug by USFDA in the upfront management of CML.

This prospective open label observational study was carried out with a sample size of 338 cases of CML

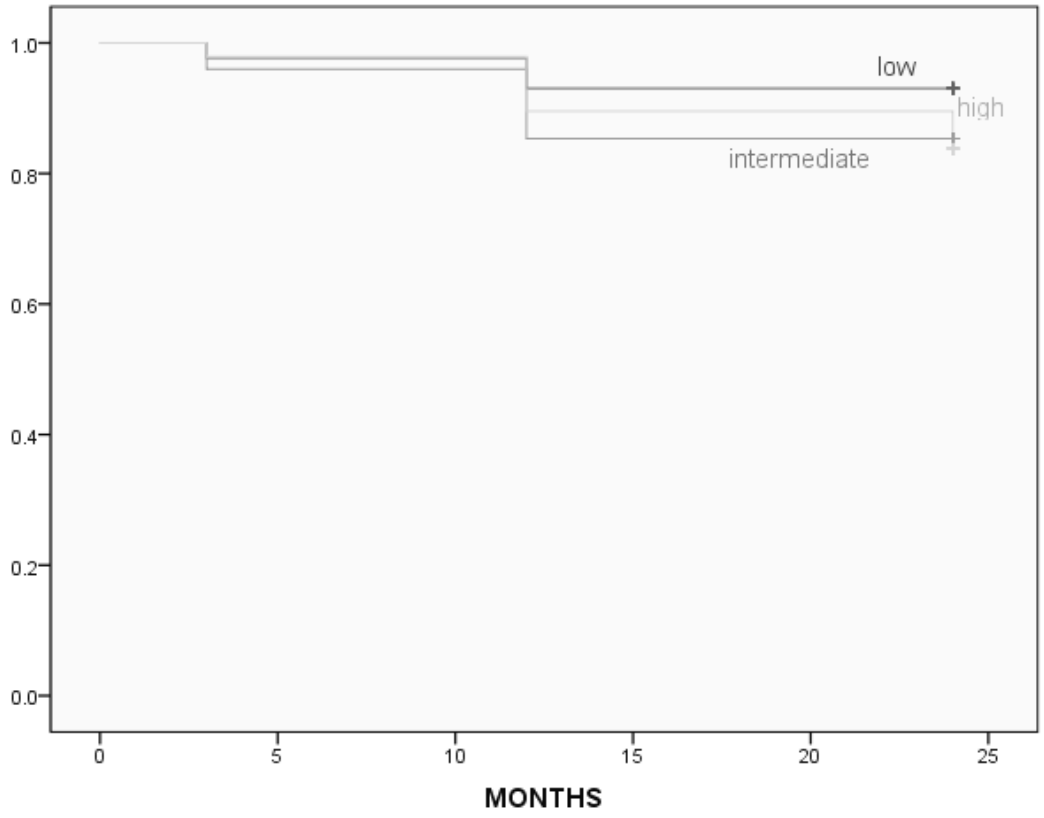

Figure 3. Progression-free survival (PFS) in patients with different severity of Sokal score.

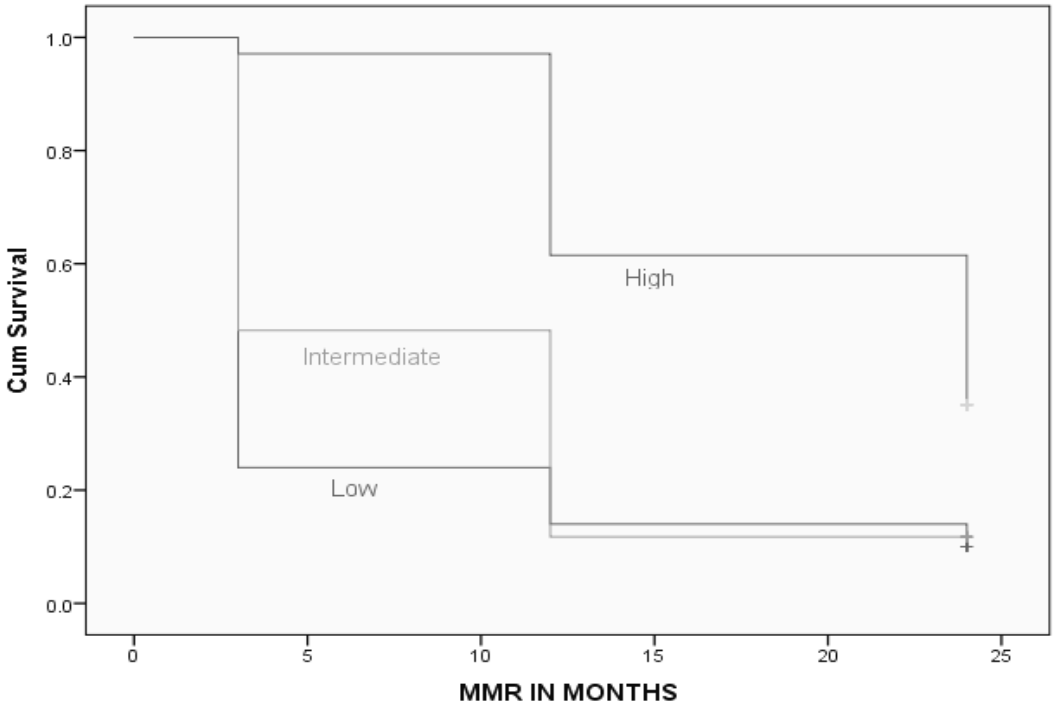

Figure 4. Cumulative achievement of MMR in patients with different severity of Sokal score.

in chronic phase of the disease (CML-CP) who were prescribed with Imatinib mesylate. Out of these patients 310 patients were qualified for inclusion in this study.

The general baseline characteristics of the patients are depicted in Table 1. Chronic myeloid leukemia (CML) is a disease seen in adults. In the western world, it occurs with an annual frequency of about 1-2/100,000 of the population and this incidence seems to be fairly constant in different countries [10]. In our study male patients constituted the major portion that is seventy seven percent similar to that of Tardieu S *et al*. [11]. This could be due to the fact that the most of the female patients don't report to the hospital because of the lower education status and lower financial capacity in our set up. The median age of the patients was 58 years in our study which was similar to the observation by Tardieu S *et al*. but different to that of Chhikara S *et al*. [11, 12]. The median time from the start of the symptoms till reporting to the hospital is long 8 months, which could again be explained due to the education and socioeconomic status.

Using the Sokal score, 43 (14%), 75 (24%), and 192 (62%) patients were divided into low, intermediate, and high-risk groups, respectively. The higher number in the high Sokal score group could be due to late reporting of the patients and lack of Haematology/ Oncology services in this region. Our findings are in line with previous studies from European population and Western population but in contrast to the studies on Chinese population by Tao *et al*., Hasford, J. *et al*. and Ylescas-Soria, J. *et al*. [13-15].

The overall PFS was 85.4% in our study which was different from the study by Hochhaus, A. *et al*. [16]. This might be due to the difference in the study region and study duration. The PFS according to the Sokal score was 93%, 85.3% and 83.8% in low, intermediate and high-risk groups, which was comparable to the study by Hochhaus, A. *et al*. [16]. This might be due to the variation in the period of observation.

All the break points were single transcript, majority of p210 (94.1%) and some cases of p190 (5.9%). Similar finding was observed in a study on Mexican subjects [17]. Though p190 break point is mostly found in Ph(+) acute lymphoblastic leukemia, a few CML cases also show this[18]. Response to imatinib was much poor in subjects having p190 break point and 50% of those cases showed disease

progression. Various other studies also demonstrated similar result [19-21].

According to Sokal score, the incidence of MMR was 90%, 88.2%, and 64.9% for low-, intermediate-, and high-risk groups, respectively ($P < 0.05$). Similar findings were seen with the study by Sokal, *et al*, Chhikara, S. *et al*. [8, 12]. But this was different to the outcome reported by Yamamoto, E. *et al.* and Kuntegowdanahalli, L. C. *et al.* [22, 23].

LIMITATIONS

The duration of follow-up was less compared to other studies. Sokal scores were primarily validated for patients on hydroxyurea or IFN-α therapy. This made it imperative to re-evaluate their significance in the current era of TKI-based first line therapy, but the results in various studies regarding this validation have been conflicting. Instead EUTOS score, which was specifically developed for the patients on TKI treatment, would have given a better picture.

CONCLUSION

The course of CML management in this region has taken a right direction after the availability of Imatinib mesylate and monitoring of the response with bcr-abl protein has revolutionised the entire management of CML in India.

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AUTHOR'S CONTRIBUTION

Prof. Truti Rekha Swain - Study hypothesis, design, data collection and analysis.
Dr. Siddhartha Goutam - Manuscript writing, data analysis.
Prof. R. K. Jena - Study hypothesis, data collection.
Prof. Niranjan Rout - Overall supervision of the study, time line management.

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Nil.

CONFLICT OF INTEREST STATEMENT

None to declare.

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