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ORIGINAL ARTICLE

Anemia requiring transfusion in breast cancer patients on dose-dense chemotherapy: Prevalence, risk factors, cost and effect on disease outcome

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Abstract

Purpose Dose-dense chemotherapy improves survival but with increased toxicity and treatment-related cost. We report the prevalence of anemia and the possible risk factors associated with chemotherapy-related anemia and determine the cost and time-delay associated with transfusion requirement in Indian patients with non-metastatic breast cancer on dose-dense preoperative chemotherapy.

Methods In this study, triple-negative breast cancer (TNBC) patients were treated preoperatively with docetaxel and cyclophosphamide alternating with epirubicin and cisplatin every 2 weeks. Patients were evaluated for anemia pre- and post-chemotherapy. We examined trends in the red cell indices, transfusion requirement, time to transfusion, as well as risk factors associated with transfusion during treatment, along with delay in treatment due to anemia and the additional cost incurred.

Results A total of 116 consecutive women with nonmetastatic TNBC were treated with preoperative chemotherapy. The median age was 44.5 years. 56.1% of patients had stage III disease. Anemia was detected at baseline in 54 (46.5%) patients with mild anemia (10–12 g/dl) in 42 (36.2%) patients and moderate anemia (8–10 g/dl) in 12 (10.3%) patients. During the course of treatment, all patients developed anemia. A total of 44 patients (37.9%) required transfusion during chemotherapy, with 55(47.4%) patients developing grade 1–2 anemia and 40 (34.5%) patients developing grade 3 anemia. The factors associated with anemia requiring transfusion were a steeper decline in hemoglobin after two cycles (OR 1.65, $p=0.02$), low-grade tumor (OR 2.48, $p=0.03$), and thrombocytopenia grade 3 or 4 (OR 4.35, $p=0.034$), of which tumor grade and thrombocytopenia remained significant in multivariate analysis. Nearly one-fourth of the study population had a delay between two cycles of chemotherapy due to anemia. A median additional cost of INR 7000 was incurred among those requiring blood transfusion.

Conclusion Anemia is a common toxicity associated with dose-dense chemotherapy during curative breast cancer treatment leading to delay in treatment and increased cost. Low-grade tumor, grade 3 or 4 thrombocytopenia, and grade 2 or higher anemia after two cycles of chemotherapy are risk factors for blood transfusions during treatment.

Keywords Anemia · Dose-dense chemotherapy · Breast cancer

Introduction

Anemia is the commonest complication encountered while treating cancer patients. It is present in 50–65% of cancer patients at the time of diagnosis [1–5] and rises to as high as 90% after completion of treatment [6]. Anemia has shown to not only affect the quality of life in cancer patients but is also associated with reduced treatment effectiveness, increased mortality, and increased transfusion requirement [5, 7–9].

Anemia in cancer patients is multifactorial and can be due to nutritional deficiencies, hemolysis, bleeding, anemia

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of chronic disease, or myelosuppressive chemotherapeutic agents [10].

Identifying factors that can predict the development of anemia requiring transfusion during treatment will help in improving supportive care and guide tailored management of patients at risk of developing severe anemia [11]. Baseline hemoglobin, body mass index (BMI), high haptoglobin, high ferritin, and glomerular filtration rate (GFR) are considered important predictors for developing anemia and subsequent transfusion [6, 11–15].

There has been renewed interest in using platinum agents in early triple-negative breast cancer (TNBC). Though the randomized trials incorporating carboplatin in neoadjuvant chemotherapy showed high pathological complete response (pCR) rates, they had a high proportion of patients experiencing myelotoxicity, including anemia and neutropenia, leading to dose omissions and incomplete delivery of all active agents [16, 17]. In this study, we aimed to assess the prevalence and risk factors for anemia requiring transfusion in patients with early TNBC receiving cisplatin with dose-dense anthracycline and taxane. We wished to assess the safety of cisplatin in this group of patients with respect to anemia requiring transfusion and the proportion of dose omissions due to the same. A higher dose completion rate would result in better compliance, complete delivery of all doses, a higher proportion of patients achieving a pathological complete response, and better survival. We also aimed to determine the cost of treating anemia, delay in treatment delivery, and its impact on disease outcome in terms of pathological response.

Methods

Study design and patients

This retrospective cohort study was done at a tertiary care referral teaching hospital in South India. We recruited 116 patients with triple-negative breast cancer from January 2017 to January 2020. All patients were treated with a regimen of dense dose chemotherapy. Patients were planned for a total of 8 cycles of chemotherapy every 2 weeks. Four cycles of docetaxel (75 mg/m2) and cyclophosphamide (600 mg/m2) were given alternating with four cycles of epirubicin (90 mg/m2) and cisplatin (60 mg/m2). The details of the clinical efficacy of this chemotherapy regimen have been reported previously [18]. The sample size was calculated using the formula $n = (Z^2 * p(1\text{-}p))/d^2$, where p is the expected prevalence of anemia requiring transfusion (Hb < 8 g/dL). The required sample size was estimated to be at least 114 patients with a precision of 0.09 (confidence interval 95%).

Patients were transfused if their hemoglobin level dropped below 8 g/dL or in case of heart failure attributable to anemia. Expenditure associated with transfusions and delay in treatment due to transfusion was also evaluated.

The study was approved by the Institutional Review Board and Ethics committee, Christian Medical College Vellore, Tamil Nadu, India (IRB number: 13960 [Retro] dated 28.04.21).

Data collection

We collected baseline demographic details such as age, gender, and residence address along with clinicopathological tumor-related characteristics such as tumor histology, tumor grade, and TNM stage. Treatment details such as the number of cycles given and the toxicity during chemotherapy were also documented. We measured the MCV, MCH, MCHC, RDW, and hemoglobin at baseline, between chemotherapy cycles and at the end of treatment. Anemia was diagnosed based on the WHO definition of Hb < 12 g/dL for women and Hb < 13 g/dL for men [19]. Neutropenia and thrombocytopenia were graded based on CTCAE v5.0. Data was collected regarding the need for transfusion, time of transfusion, and the number of packed cells transfused. Dose delay was defined as a delay of > 2 days from the expected administration of a given cycle. Menopause was defined as amenorrhea for at least 12 months prior to the initiation of the first cycle of chemotherapy.

Statistical analysis

We used mean and standard deviation (SD) to summarize variables with a normal distribution and median and interquartile range (IQR) for variables with a non-normal distribution. Univariate analyses were carried out using appropriate parametric/nonparametric tests. Quantitative and qualitative variables were transformed, when appropriate, into ordinal variables, using clinically relevant cutoff points. The results of univariate and multivariate analyses are presented with adjusted odds ratio, 95% confidence intervals (95% CI), and p value. Receiver-operating characteristic (ROC) analysis was used to assess the performance of various variables as tests to predict transfusion requirement. The area under the curve (AUC) was used to summarize the diagnostic accuracy. An AUC of 0.5 corresponds to chance, and 1.0 corresponds to perfect test accuracy. Significance levels were defined as a p value less than 0.05.

The primary outcome assessed in this study was the proportion of patients who developed anemia requiring transfusion during treatment. The major secondary endpoints assessed were the risk factors for anemia requiring transfusion, its impact on the pathological response, the

additional cost incurred due to transfusion, and delay in the administration of chemotherapy doses. All analyses were performed using IBM SPSS Statistics 25 software and R (Version 4.1.2).

Results

Baseline characteristics and prevalence of anemia

The median age of the population was 44.5 years (range 45–67 years). Stage II disease was seen in 41.1% of patients and 56.1% had stage III disease. All 8 doses of chemotherapy were administered in 86% of patients. Delivery of six out of the eight planned doses was achieved in 98% of patients.

Nearly half (47.4%) of all patients were anemic at the time of diagnosis with 44 (37.9%) patients having CTCAE v5.0 grade 1 anemia, 10 (8.6%) patients having grade 2 anemia, and 1 (0.9%) patient having grade 3 anemia. All of these patients developed anemia during the course of chemotherapy. Table 2 shows the hematological toxicities related to the chemotherapy. Only one patient had undergone detailed evaluation for etiology of anemia, and only 24 (20.6%) patients received any form of iron supplementation.

Transfusions

A total of 44 (37.9%) patients required at least 1 unit of blood transfusion during chemotherapy. A total of 73 units of packed red cells were transfused in the entire study population with a maximum of 4 units transfused for an individual patient. There was a mean rise of 1.7 ± 0.5 g/dl in hemoglobin level following transfusion. The median time to transfusion was 91 days(IQR 70–118). This corresponds to having completed 6 cycles of chemotherapy.

Risk factors

Patients in the transfused and non-transfused groups had comparable mean age, disease status, and hematological characteristics. Differences were noticed between both the groups with respect to the number of cycles received, menopausal status, and grade of tumor (Table 1).

Table 1 Baseline characteristics

Characteristic	Not transfused ($n=72$)	Transfused ($n=44$)
Age (years)*	42.2 ± 8.2	45.1 ± 9.3
Stage ($n=107$)		
Early stage (I and II)	28 (43.8%)	19 (44.2%)
Locally advanced (Stage III)	36 (56.2%)	24 (55.8%)
Grade of tumor ($n=112$)		
Low-grade (grade I and II)	16 (23.2%)	19 (44.2%)
High-grade (grade III)	53 (76.8%)	24 (55.8%)
Cycles completed ($n=114$)		
7 or less	7 (10%)	9 (20.5%)
Completed all 8 cycles	63 (90%)	35 (79.5%)
Baseline hemoglobin (mg/dl)*	11.8 ± 1 .3	11.6 ± 1.1
Baseline MCV (fL)*	83.6 ± 7.5	84.6 ± 7.8
Baseline MCH (pg)*	27.0 ± 3.1	27.3 ± 3.1
Baseline MCHC (g/dL)*	32.2 ± 1.3	32.2 ± 1.3
Baseline RDW *	15.1 ± 3.8	14.4 ± 1.8
Menopausal status		
Premenopausal	52 (72.2%)	25 (56.8%)
Postmenopausal	20 (27.8%)	19 (43.2%)
ECOG score		
0 score	50 (69.4%)	32 (72.7%)
1–2 score	22 (30.6%)	12 (27.3%)
Anemia at diagnosis		
Grade I (10–12 g/dl)	24 (33.3%)	20 (45.4%)
Grade II (8–9.9 g/dl) and grade III (6.5–7.9 g/dl)	7 (9.6%)	4 (9.1%)

*Mean and standard deviation

Table 2 Hematological toxicity of chemotherapy

Characteristic	Not transfused ($n=72$)	Transfused ($n=44$)
Anemia after last cycle* ($n=113$) **		
Grade I	27 (37.5%)	4 (9.1%)
Grade II	40 (55.6%)	27 (61.4%)
Grade III		13(29.5%)
Drop in hemoglobin after 2 cycles*** (mg/dl)	1.25 (0.42–1.97)	1.75 (1.00–2.40)
Thrombocytopenia*		
Low-grade (grade I and II)	40 (55.5%)	24 (54.5%)
High-grade (grade III and IV)	3 (4.2%)	7 (15.9%)
Neutropenia*		
Low-grade (grade I and II)	13 (18.0%)	9 (20.4%)
High-grade (grade III and IV)	8 (11.1%)	11 (25.0%)

*CTCAE v5.0 grading

**2 patients were not anemic at the end of chemotherapy. Data missing for 3 patients in the Not transfused group

***Median and IQR

A greater percentage (54.5% vs 43%) of patients were anemic at the time of diagnosis in the transfusion group; however, this difference was not statistically significant. The mean hemoglobin done prior to each cycle began to diverge significantly ($p=0.003$) between the transfused and non-transfused groups at cycle 2 and remained divergent till the end of all chemotherapy cycles. The hemoglobin prior to cycle 2, although not an ideal test to determine who would get transfused, with an area under the curve (AUC) of 0.658 in the receiver-operating characteristic (ROC) curve, had a reasonable sensitivity and low specificity of 70% and 30%, respectively, at hemoglobin cutoff of 10 g/dL. At a cutoff of 9 g/dL, the Hb post cycle 2 had a high sensitivity of 93% but a very low specificity of 7%. Hemoglobin post cycle 4 had the best test performance with an AUC of 0.826, but had sensitivity and specificity of 48% and 52%, respectively, at Hb cutoff of 10 g/dL and 86% and 14%, respectively, at Hb cutoff of 9 g/dL. The ROC curves are shown in Graph 2. Other parameters including baseline Hb, MCV, MCH, MCHC, and RDW were not good predictors of transfusion (Table 3).

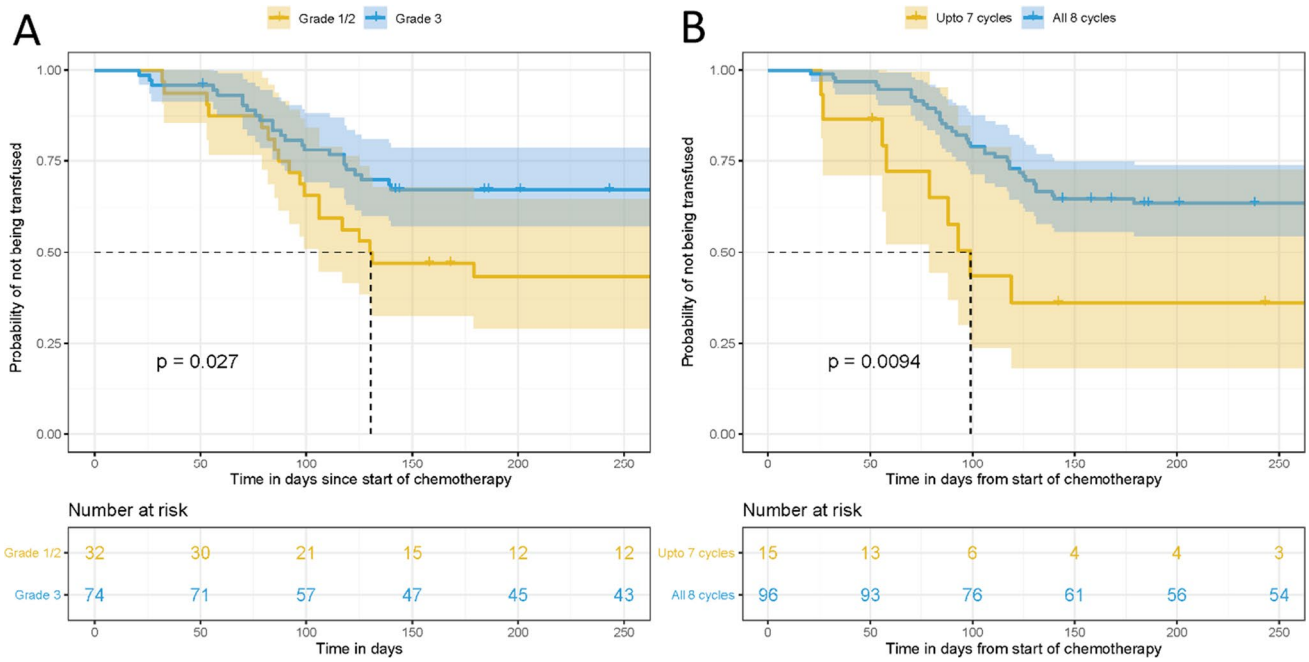
In univariate analysis, the patients who had a higher odds of transfusion were those who had a steeper absolute drop (1.75 g/dL vs. 1.25 g/dL) in hemoglobin after 2 cycles (OR 1.65 (1.09–2.49), $p=0.017$), high-grade thrombocytopenia (G3 and above) (OR 4.35 (1.06–17.83), $p=0.034$), and low-grade tumor (G1/2) (OR 2.48 (95% CI 1.08–5.68), $p=0.025$). Graph 1 (Time to event analysis) shows patients with low-grade tumors were more likely to be transfused earlier. No other baseline factor was significantly associated with transfusion requirement. In multivariate analysis with a model incorporating menopausal status, drop in hemoglobin after 2 cycles, grade of tumor, and grade of thrombocytopenia, the last 2 factors were significantly associated with transfusion requirement (Table 3).

Impact of anemia

Impact of anemia was assessed in terms of delay in treatment and cost associated with transfusion.

In cox regression analysis (Graph 1), there was a statistically significant difference in the time to transfusion between those who had less than 8 cycles vs. those who completed all 8 cycles (log rank p value 0.009). We surmised that this could be explained, as the last few cycles may have been omitted in those patients who developed severe anemia and required transfusion. However, analysis of the documented reasons for discontinuation did not correlate well with this hypothesis. Among the 19 patients who did not receive all 8 cycles, only a minority had dose omissions due to anemia. The other reasons for dose omissions were grade 3 adverse events like thrombocytopenia, fatigue, AKI, and logistical issues at the peak of the COVID-19 pandemic.

A total of 27 patients (23.2%) had a delay between two cycles of chemotherapy due to anemia. Delay ranged from a minimum of 2 days to a maximum of 16 days with a median delay of 6.5 (IQR 4.2–8.5) days. Treating triple-negative breast cancer with the above mentioned regimen costs approximately INR 170,000 for 8



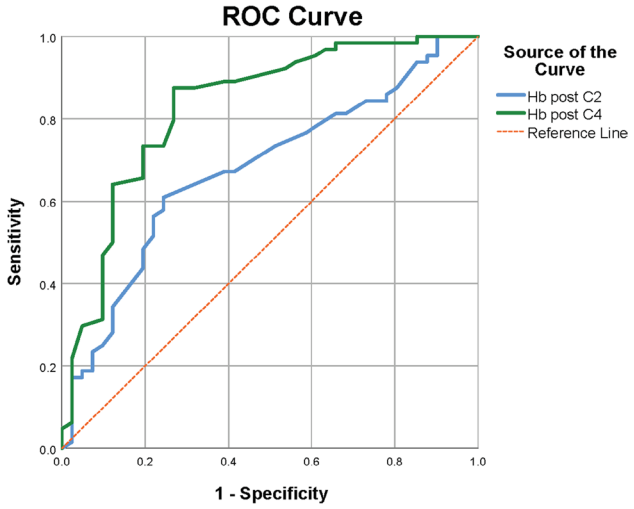
Graph 1 Time to transfusion from start of chemotherapy stratified by grade of tumor (graph **A**) and number of cycles (graph **B**)

Table 3 Factors associated with risk of transfusion requirement

Characteristic	Odds ratio (95% CI)	Unadjusted *p* value	Adjusted *p* value
Age	1.04 (0.99–1.09)	0.09	-
Drop in hemoglobin after 2 cycles(1.75 g/dL vs. 1.25 g/dL)	1.65 (1.09–2.48)	**0.017**	0.201
Baseline hemoglobin	0.89 (0.67–1.21)	0.474	-
Baseline MCV	1.02 (0.99–1.07)	0.533	-
Baseline MCH	1.02 (0.91–1.16)	0.691	-
Baseline MCHC	0.98 (0.74–1.29)	0.868	-
Baseline RDW	0.90 (0.76–1.07)	0.235	-
Hemoglobin post cycle 2	1.74 (1.21–2.51)	**0.003**	**-**
Stage ($n=107$) (locally advanced vs. early stage)	0.98 (0.45–2.14)	0.561	-
Grade of tumor ($n=112$) (low grade vs. high grade)	2.48 (1.08–5.68)	**0.025**	**0.014**
Cycles completed ($n=114$) (8 cycles vs. 7 or less)	0.43 (0.15–1.26)	0.100	-
Menopausal status (postmenopausal vs. premenopausal)	1.98 (0.89–4.35)	0.067	0.775
ECOG PS (1–2 vs. 0)	0.85 (0.37–1.96)	0.437	-
Neutropenia grade 3/4	2.67 (0.98–7.27)	0.070	-
Thrombocytopenia grade 3/4	4.35 (1.06–17.83)	**0.034**	**0.022**

cycles (including generic drugs, generic pegfilgrastim, professional charges, and laboratory investigations) if there are no grade 3/4 adverse events. A median cost of INR 7000(IQR 7000–14,000) was spent additionally on transfusion.

Transfusion requirement, delay in chemotherapy, baseline anemia, and pre-op hemoglobin did not have an impact on the early treatment outcome, assessed in terms of pathological complete response (T0/Tis N0). Data on the disease response rates and survival have been reported separately [18].



Graph 2 ROC curves for transfusion requirement

Discussion

This study describes the prevalence of anemia and transfusion practices in the preoperative treatment of early TNBC. Dose-dense chemotherapy has been shown to improve clinical outcomes in breast cancer patients [20] but is associated with a higher incidence of anemia [21]. The incidence of anemia was found to be 47.4%, similar to other studies conducted in breast cancer patients [1–5]. Transfusion requirement in our population was higher than expected. At least 1 unit of packed cells was transfused in 37.9% of the patients as compared to other studies conducted in breast cancer patients – 28.1% in the study by Moebus et al. [21] and 11.4% in the study by Leyland-Jones et al. [22]. This could be attributed to the added toxicity of cisplatin in the regimen used in our study population [23]. A greater percentage of patients who were transfused were found to be anemic at the time of diagnosis. Baseline anemia and baseline hemoglobin have been identified to be independent risk factors for transfusion in multiple studies [11–14]. However, in our study, the association was not found to be statistically significant.

Hemoglobin after cycle 2 and after cycle 4 was found to be reasonable predictors for transfusion requirement later on with high sensitivity but low specificity at cutoffs of 9 and 10 g/dL. The patients who had a steeper drop in hemoglobin by cycle 2 (1.75 g/dL) had a greater odds of transfusion later. The above parameters could possibly help us in identifying patients who might require transfusion early on but need to be further investigated in prospective studies.

Patients who developed grade 2 or higher thrombocytopenia during treatment were also more likely to be transfused. This could be explained by a predilection among these patients for greater myelosuppression or poor marrow reserve at the outset. Patients with low-grade tumors were more likely to get transfused. This observation has been documented in previous studies on anemia in breast cancer [24]. Serum hepcidin levels are significantly higher and negatively correlated with hemoglobin in breast cancer patients with anemia, pointing to chronic inflammation as a major driver of anemia in these patients [25]. The indolent, slow-growing nature of low-grade tumors, delays diagnosis possibly by months to even years in some cases, especially in low resource settings without breast cancer screening programs, likely predisposing these patients to prolonged exposure to elevated levels of hepcidin [26]. Hepcidin acts by blocking intestinal iron absorption, leading to low iron stores, and impairment of macrophage iron recycling, causing iron-deficient erythropoiesis and anemia [27]. This in turn leads to the development of anemia of chronic disease or nutritional deficiencies like iron deficiency in these patients at baseline, making them more susceptible to developing severe anemia requiring transfusion during the course of treatment.

The financial toxicity of chemotherapy-related anemia was assessed in terms of added cost of transfusion and delay in treatment. Time burden associated with outpatient transfusion in cancer patients has been studied previously [28]. We found that nearly one fourth of our patients had a delay of at least 2 days in their chemotherapy schedule. The direct cost of transfusion and the indirect cost due to delay in treatment lead to an increase in the overall cost of treatment of breast cancer.

The main limitations of our study are the small sample size and retrospective study design. The study included only patients with triple-negative breast cancer. As the patients were given a platinum-based regimen, the transfusion requirement and degree of anemia might be exaggerated as compared to treatment regimens for other types of breast cancer where platinum-based chemotherapy is generally not used. Baseline pre-treatment evaluation of anemia was incomplete and non-uniform in the majority, and therefore the etiology of anemia was not elucidated in our study population.

Conclusion

Anemia requiring transfusion is a common toxicity of dose-dense chemotherapy. Patients experience substantial time burden due to delay along with additional financial toxicity of treatment of anemia due to chemotherapy. Hemoglobin value and absolute decrease in hemoglobin after the initial few cycles could predict the need for transfusion. Low-grade tumors and development of thrombocytopenia were associated with transfusion requirement.

Author contribution The authors had the following contributions:

Author(s) Name	Responsibilities								
	Research and Study design	Data collection & Analysis	Laboratory analysis	Interpretation and conclusion	Preparation of Manuscript	Review of Manuscript	Guide and critical revision	Administration	Technical Support
Parth Sharma	✓	✓	✓	✓	✓	✓			
Josh T. Georgy	✓	✓	✓	✓	✓	✓			✓
Anand G. Andrews	✓	✓	✓	✓	✓	✓			
Ajoy O. John	✓			✓	✓	✓			✓
Anjana Joel	✓			✓		✓			✓
Raju T. Chacko	✓			✓		✓			✓
Prasanna S. Premkumar	✓	✓				✓			✓
Ashish Singh	✓	✓		✓	✓	✓	✓	✓	✓

Data availability Data is available upon request.

Code availability Not applicable.

Declarations

Ethics approval The study was approved by the Institutional Review Board and Ethics committee, Christian Medical College Vellore, Tamil Nadu, India (IRB number: 13960 [Retro] dated 28.04.21).

Consent to participate The patients consented for treatment and collection of data prior to initiation of treatment.

Consent for publication As this was a retrospective study consent for publication was waived by the Institutional Ethics Committee.

Competing interests The authors declare no competing interests.

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