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Original Article

Experience of the Administration of First Dose IV Zoledronate at Queen Elizabeth Hospital

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Abstract

Background: Osteoporosis affects nearly 3 million people in the UK, with bisphosphonates forming the mainstay of treatment. While the side effect profile of zoledronate is well-documented, adherence to prescribing guidance and specific population outcomes warrant further investigation. Our objectives were to assess whether zoledronate was prescribed correctly in accordance with guidance and evaluate the side-effect profile with attention to demographic variables.

Methods: A retrospective analysis of 68 patients receiving their first dose of zoledronate at Queen Elizabeth Hospital, Birmingham (QEHB), between January and December 2021. Strict inclusion and exclusion criteria were applied. Patient records were reviewed for adherence to guidance, including pre-infusion checks and indication for treatment. Side effects were documented through post-infusion questionnaires. This timeframe was selected to capture a full year of prescribing patterns and ensure consistency in available data.

Results: Among 68 patients (13 males, 55 females; age range 28-92), 96% were prescribed zoledronate for appropriate indications. Vitamin D was checked in 93%, and 100% underwent dual-energy X-ray absorptiometry (DXA) scans. However, only 16% had Fracture Risk Assessment Tool (FRAX) scores calculated. One patient received the infusion despite an estimated glomerular filtration rate < 35 mL/min. Side effects were reported in 37%, primarily bone/joint pain. Statistical analysis did not find a significant correlation between age, sex, or ethnicity and side-effect frequency ($P > 0.05$). Age appeared to influence post-dose symptoms, with older patients experiencing fewer side effects. Ocular symptoms were reported in 2 cases, and details of these were analyzed. South Asian females reported a higher incidence of side effects, but this observation remains exploratory due to the small sample size.

Conclusion: This audit has shown that zoledronate is being prescribed in accordance with guidance at QEHB. Treatment is offered after systematic checks of biochemical parameters. However, the low rate of FRAX score calculation (16%) raises concerns about the completeness of fracture risk assessment. A potential explanation is the reliance on DXA scanning or clinical judgment, and a lack of transfer of information from primary care. Side effects reported are covered in patient information leaflets. Given that side effects were assessed 16 weeks post-infusion, recall bias should be considered a limitation. Further research is needed to ascertain predictors for subsequent adverse effects following infusion. Zoledronate prescription was largely in line with guidance, though notable gaps in fracture risk assessment were observed. The side effect profile aligned with existing literature, and demographic variations in adverse events should be interpreted cautiously given the sample size constraints.

Keywords: Audit, bisphosphonates, fragility fracture, osteoporosis, zoledronic acid

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Introduction

Over 3 million people in the UK are living with osteoporosis.[1] It develops slowly over several years and is often only diagnosed when a fall or sudden impact causes a bone to break (fracture). The most common injuries in people with osteoporosis are broken wrists, hip fractures, and vertebral fractures. Osteoporosis is not usually painful until a bone is broken, but spinal fractures are a common cause of long-term pain. Women are at greater risk, with 50% of women over 50 years and 20% of men experiencing osteoporotic fractures during their lifetime. There are over 500 000 fragility fractures per year and more than 100 000 of these are serious vertebral or hip fractures. The burden is significant both for patients and healthcare systems.

Osteoporosis becomes more common as part of the normal aging process. Being postmenopausal, having an early menopause, and lower body mass index (BMI) are all risk factors. Certain medications

used to treat chronic inflammatory conditions, such as steroids can also predispose one to osteoporosis. A bone density scan compares an individual's bone density with that expected for a young healthy adult or a healthy adult of the same age, gender, and ethnicity. The difference is calculated as a standard deviation score, which measures the difference between their bone density and the expected value. The difference between the measurement and that of a young healthy adult is known as a T score, while the difference for someone of the same age is known as a Z score.

Initially, a focus is placed on checking levels of calcium and vitamin D. This is achieved via optimizing diet or supplements. Bisphosphonates form the mainstay of pharmacological treatment by slowing the rate of bone breakdown in the body by inhibiting osteoclast-mediated bone resorption. This maintains bone density and reduces the risk of a broken bone.[2] They are administered as a tablet or in liquid form injected intravenously (IV). Bisphosphonates usually take 6-12 months to work.[3] Zoledronate, a once-yearly intravenous bisphosphonate, has been in use for over 2 decades and offers an effective alternative for patients unable to tolerate oral formulations. There are some side effects, such as myalgia, arthralgia, and a flu-like illness. The most rare and serious side effect is osteonecrosis of the jaw (ONJ). While its side-effect profile is well-established, variations in adherence to prescribing guidance and demographic influences on adverse events remain areas for further research.

Main Points

- Zoledronate Prescription: Adherence to National Osteoporosis Guideline Group guidelines was observed in 96% of cases at Queen Elizabeth Hospital, Birmingham, ensuring appropriate use.
- Side effects: 37% of patients reported post-infusion symptoms, with bone/joint pain being the most common.
- Demographic insights: South Asian females reported a higher incidence of side effects (63%) compared to other groups.
- FRAX Score calculations: Only 16% of patients had a complete FRAX risk assessment, highlighting an area for improvement.
- Safety profile: No cases of osteonecrosis of the jaw or atrial fibrillation were reported, aligning with existing safety data.

Objectives

The National Osteoporosis Guideline Group (NOGG) has specific standards regarding the prescription of zoledronate.[4-6] Morbidity is high in patients with osteoporotic fractures. There is a high mortality rate after discharge from the hospital and increased risk of future fractures.[7] Hip fractures alone account for £1.5 billion in hospital costs, excluding social care costs. Additionally, neck of femur fractures have a high mortality rate of approximately 20%-30% at 1 year.[8] Therefore, the care pathway must be shifted to a proactive rather than reactive approach.

To investigate whether zoledronate was being prescribed correctly at a large tertiary center, the proportion of patients given IV zoledronate for an appropriate indication outlined by NOGG was assessed. In addition, compliance with recommended pre-infusion checks was verified. Furthermore, there was an analysis of the proportion of patients with complete FRAX assessments. By doing so, overall prescribing was summarized, and its potential impact on the frequency of side effects was explored as a secondary question.

Material and Methods

Study Design and Participants

Data in this audit were collected from a single center: Queen Elizabeth Hospital Birmingham (University Hospitals Birmingham NHS Trust). Patients were recruited from the Fracture Liaison Service (FLS), who had had at least 1 dose of IV zoledronic acid and had follow-up in the form of a post-infusion questionnaire. Ethical approval for the audit was granted by the University Hospitals Birmingham NHS Trust Clinical Governance team under protocol number Q784389 on 10/09/2022. The study was registered on the trust audit portal. Inclusion criteria focused on osteoporosis, fragility fractures, and glucocorticoid-induced osteoporosis. Exclusion criteria included patients on other bisphosphonates, those with malignancies, and patients with incomplete data. The total number of patients included was 68, with all giving written consent to use their data.

Data Collection

Data on these patients from the period of January to December 2021 was retrospectively reviewed. Pertinent information was obtained using electronic health records from trust computer systems (PICS and Portal). This timeframe ensured a consistent dataset while capturing the most recent full prescribing cycle that was yet to be analyzed. This period was selected because of the availability of standardized post-infusion questionnaires and electronic records for consistent data collection. The questionnaires allowed a thorough assessment of the onset, duration, and frequency of side effects through a tick-box method. Also, there was space for longer answers where patients could express their views relating to whether they had the relevant pre-infusion checks and if they were given sufficient information about zoledronate. Questionnaires were sent to patients 16 weeks after their first dose of IV zoledronate. These were filled out by patients and sent back to clinical nurse specialists (CNS) as part of the care pathway. Questionnaires included multiple-choice and open-ended responses regarding symptom onset, duration, and severity. Potential recall bias was acknowledged.

The information collected was coded into a predesigned digital extraction form in Excel. This was done independently by two authors (AS & BKSS) to ensure that the results were accurate. Again, this was verified by a separate senior reviewer to avoid error. The focus was on the pre-infusion checks, i.e., vitamin D and calcium correction, measurement of renal function (estimated glomerular filtration rate—eGFR), calculation of FRAX score, and a complete dental checkup. Zoledronate is contraindicated in patients with renal impairment (eGFR < 35 mL/min). Furthermore, each patient's indication for receiving zoledronate was tracked, and its alignment with NOGG guidance (osteoporosis/glucocorticoid-induced osteoporosis) was assessed.[9,10] Finally, the side-effect profile reported by patients was compared to the existing evidence to see if the quality of prescribing was having any effect on the prevalence of adverse effects.

Statistical Analysis

Statistical analyses were conducted using SPSS v27 (IBM SPSS Corp.; Armonk, NY, USA). Descriptive statistics summarized patient demographics and biochemical parameters. Categorical variables were expressed as percentages, while continuous variables were reported as mean ± standard deviation. Comparisons of side effects by age, sex, and ethnicity were analyzed using chi-square tests and logistic regression. Missing data, such as absent vitamin D levels, were accounted for using sensitivity analyses. A *P*-value <.05 was considered statistically significant.

Results

Sixty-eight patients were included according to the strict inclusion criteria. There were 55 female and 13 male patients. The average age of participants was 70.8 (range 28-92 years). Patients were of all ethnicities including Caucasian, Asian, and Mixed races. The modal age range was between 70 and 79 years. Characteristics of participants are displayed in Table 1.

Pre-Infusion Checks

As part of the checklist for initiating bone metabolism medication, all patients must have their vitamin D, calcium, and eGFR measured prior to starting treatment. Patients are also advised to have 1 dental checkup each year. Adherence to this guidance is summarized in Figure 1.

In the cohort, all patients had their eGFR and calcium measured. The average calcium was 2.43 mmol/L (range 2.22-2.64 mmol/L), essentially being in the normal corrected range. For eGFR, the average was 76.9 mL/min/1.73m^2. However, here the range was from 30 to >90 mL/min/1.73 m^2. Zoledronate is only licensed for an eGFR >35, so there was an error in prescribing for 1 patient due to some unknown factor. Vitamin D was measured in 93% (63/68) of the patients. In those that had vitamin D measured, the average level was 75 nmol/L, with all patients having a pretreatment level of more than 50 nmol/L. Five patients did not have vitamin D levels assessed pre-infusion. Among them, 3 experienced mild side effects. The patient prescribed zoledronate with an eGFR <35 mL/min was closely monitored, with renal function improving within 6 weeks of the infusion, suggesting a transient decline likely unrelated to the drug.

Indication and Fracture Risk

According to NOGG recommendations, 65 out of 68 patients were given IV zoledronate for a correct indication. The remaining 3 cases received the infusion for osteogenesis imperfecta, Paget's disease, and osteopaenia (familial osteoporosis). While Paget's disease was not an indication for zoledronate in the NOGG guidance, it was present in this particular hospital's trust guidelines (Table 2). Younger patients primarily had secondary osteoporosis conditions such as osteogenesis imperfecta and glucocorticoid-induced osteoporosis

Approximately one-sixth of the cohort underwent a complete fracture risk assessment using the FRAX tool. All patients coming through the FLS had a FRAX score calculated, and these were shown to be above the intervention threshold for bisphosphonate therapy. The large number of patients who did not have a FRAX score calculated were from the metabolic bone disease database. In contrast to fracture risk, 100% of patients had bone density checked in the form of a DEXA scan.

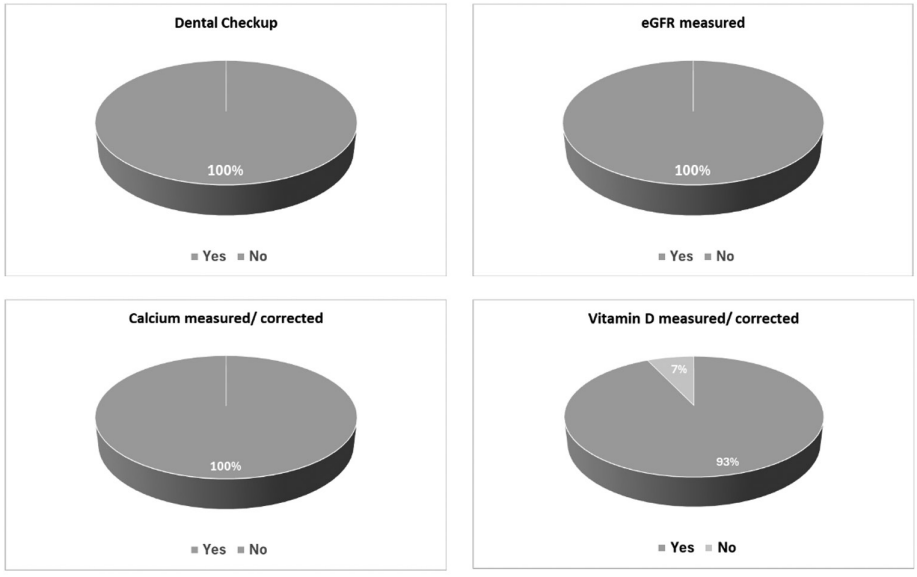

Figure 1. Adherence to pre-infusion checks. Legend: Pie charts illustrating the proportion of patients undergoing pre-infusion checks. (A) Dental checkup, (B) eGFR measurement, (C) Serum calcium measurement, (D) Vitamin D measurement.

Side Effects

Just over a third (37%) of patients reported side effects after zoledronic acid infusion. Of the 25 patients reporting side effects, bone/joint pain was the most common complaint with 18 cases (72%). This was closely followed by myalgia and headaches (Table 3). Critically there were no cases of ONJ or atrial fibrillation. Two patients reported ocular side effects, including conjunctivitis and episcleritis. Both conditions resolved within 1 week with conservative management, including artificial tears and NSAIDs.

Table 1. Baseline Characteristics

Baseline Characteristic	No. Patients (%)
Sex	
Females	55 (81)
Males	13 (19)
Ethnicity	
Caucasian	55 (81)
Asian	8 (12)
Afro-Caribbean	0 (0)
Mixed	5 (7)

Table 2. Breakdown of Indications

Indication	Number
Fragility fracture	17
Osteoporosis on DEXA	25
Fragility fracture + Osteoporosis of DEXA	23
Osteopenia	1
Osteogenesis imperfect	1
Paget's disease	1

Table 3. Reported Side Effects from Patient Questionnaires

Symptom	No. Patients Reporting Symptom
Headache	9
Dizziness	5
Sickness/vomiting	5
Diarrhea	3
Muscle pain	12
Bone/joint pain	18
Fever/chills	7
Irregular heart rhythm	0
Swelling/redness/itching to eyes	2
Pain in ear/discharges	0
Pain in mouth/sores	3
Pain in thigh	7
Other symptoms	9

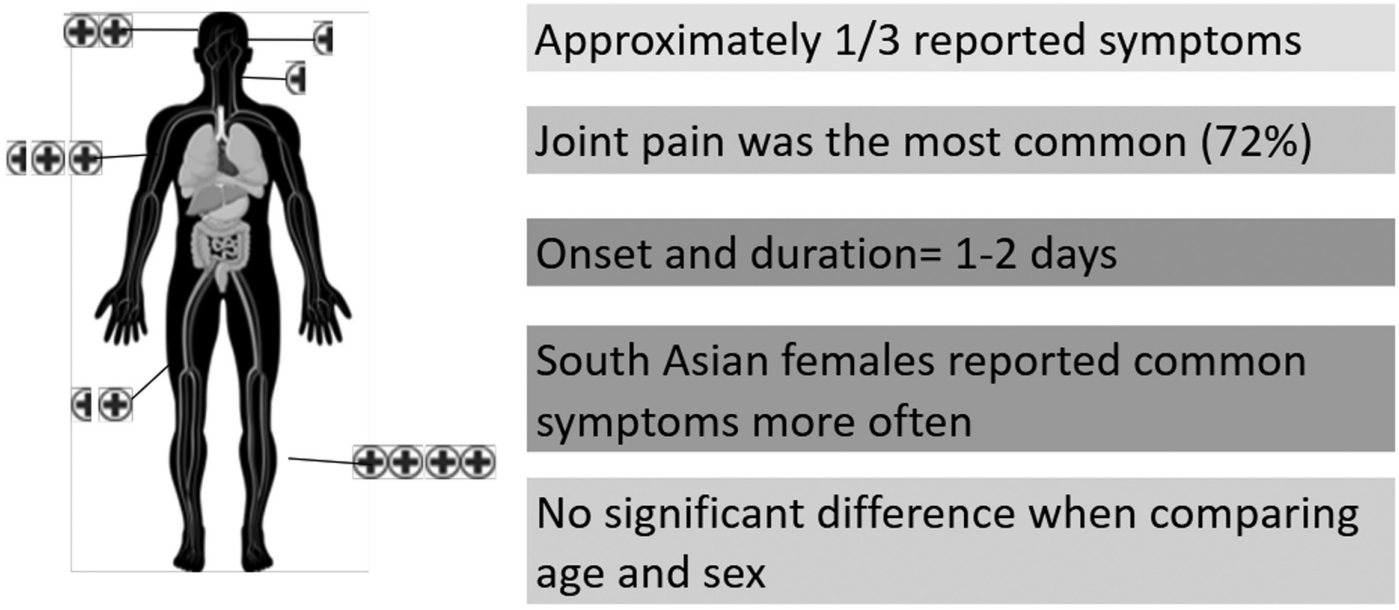

Figure 2. Schematic representation of most frequently reported side effects. Legend: The figure depicts the most common side effects by location. The number of plus symbols corresponds to how commonly these side effects were observed.

Other symptoms mentioned included fatigue, dehydration, soreness (arm), and back and hand pain. The most common onset of symptoms was after 1-2 days, and frequently this lasted 1-2 days as well (Figure 2). The spread of data showed that the duration of symptoms was likely to be for short or longer periods rather than intermediate periods (Figure 3).

The factors of age, sex, and ethnicity were compared to assess their effect on the incidence of side effect. The characteristics of those with no side effects and those who had symptoms were collected as part of the data. There were 25 patients with side effects and 43 without. Examining sex showed minimal differences in the reporting of side effects. In the group with side effects, 84% were female, and in those without, 79% were female. It is important to bear in mind that most patients were female.

Similarly, for age there were no significant differences in percentages for both groups. An observation was that side effects were more frequent in the 60-70 year range, but this is possibly a correlation rather than pathological, as most patients receiving the drug were in this age range. This is likely due to treatment distribution rather than an age-related risk factor.

Subsequently, the number in each group was stratified by ethnicity. For Caucasian and Mixed race patients, the proportion of patients in each group was somewhat similar. However, among Asians, they formed 20% of the group with side effects but only 7% of those without adverse effects. Five out of 25 in the side effects group were Asian, more than the three without side effects, despite the former group being smaller in number. What is more is that these were all female patients from the subcontinent region. Reflecting back, the overall incidence of side effects (37%) contrasts with those in the Asian population, where more patients reported side effects than did not (5/8—63%); however, this was not statistically significant ($P > .05$).

Discussion

Overall, zoledronic acid is prescribed appropriately at QEHB. Treatment is offered after systematic checks of biochemical parameters, although vitamin D checks did not occur in a minority of patients. Usage of this form of bisphosphonate is particularly useful in those unable to tolerate and comply with the needs of oral alendronate. In patients who fail initial treatment, intravenous zoledronate provides a practical alternative. The prevalence of side effects reported matches the advice given to patients via leaflets by the CNS. There were no cases of ONJ or atypical femoral fractures. Nevertheless, reconsidering annual dental checks is premature, as long-term data on ONJ are lacking. Future research should focus on personalized screening rather than general guideline alterations, given the <1/10 000 risk of ONJ in osteoporosis patients. This practice may overburden patients and healthcare systems and is better suited for high-risk populations, such as cancer patients receiving high-dose bisphosphonates. Zoledronate has been shown to be very safe in patients with osteoporosis, with less severe side effects compared to other bisphosphonates such as alendronate.[11]

The data aligns with previous findings, such as Reid et al,[12] indicating that post-infusion

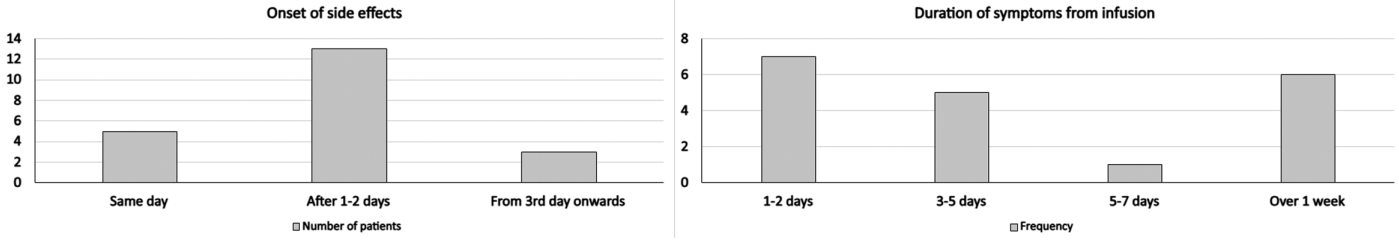

Figure 3. Onset and duration of side effects. Legend: Bar charts plotting—(A) Onset of side effects, (B) Duration of side effects.

symptoms decline with increasing age. This may reflect reduced immune responsiveness or changes in bone turnover in older individuals.

Further research is needed to ascertain predictors for side effects following infusion, as the audit suggests South Asian females may be at greater risk of experiencing side effects. This is in line with the findings of the Horizon Pivotal Fracture trial. Reid et al[12] found that the acute phase response was more common in non-Japanese Asian females. The overall prevalence of side effects in the study was also very similar to results published in this randomized controlled trial. This will enable us to identify what class of drugs is likely to suit patients, to adopt a more personalized targeted form of care.

A reason for the low number of fracture risk assessments could be attributed to the fact that often there is inconsistency between the information systems of primary and secondary care. As a result, it was believed that many will have had a FRAX score calculated by their general practitioner but were not visible to hospital staff. Many patients had fragility fractures, making FRAX scoring less relevant for treatment decisions. Additionally, primary care FRAX calculations were often not accessible in hospital records, leading to under-documentation. Improving the availability of data is key when managing patients with osteoporosis, to ensure the best management strategy. All patients also had DEXA scans, which could possibly have rendered the calculation of FRAX scores inconvenient, as it could have delayed treatment. Furthermore, a large proportion of patients had fragility fractures, pathognomonic for osteoporosis, so there may have been no need for this. Still, it is important to abide by guidance as strictly as possible. This will require effective communication through multidisciplinary management, including specialists such as endocrinologists, chemical pathologists, rheumatologists, and orthogeriatricians to name a few.

This study has several limitations that should be acknowledged. Firstly, the retrospective design relies on existing medical records and post-infusion questionnaires, which may introduce information bias or missing data. In addition, the post-infusion survey was conducted at 16 weeks, which may introduce recall bias. Literature suggests that most acute-phase reactions occur within days; therefore, the true side effect incidence could be underestimated. For instance, not all patients had comprehensive fracture risk assessments documented, and certain details, such as patient-reported outcomes, may be underreported. Prospective studies with standardized data collection would mitigate these limitations.

Secondly, the sample size of 68 patients is relatively small, particularly for subgroup analyses of demographic factors such as ethnicity and age. Demographic findings should be interpreted cautiously due to the limited sample size. While South Asian females showed a higher side-effect rate, this is an observational trend rather than a definitive conclusion. Although the findings align with published literature, larger cohorts are needed to validate observations regarding demographic influences on side-effect profiles, such as the higher prevalence of adverse events in South Asian females.

Additionally, the study was conducted at a single tertiary center, limiting the generalizability of the results to other healthcare settings or populations. Variability in prescribing practices, patient demographics, and healthcare systems may lead to different outcomes elsewhere. Multicenter studies would provide broader insights.

Finally, long-term outcomes, such as adherence to subsequent zoledronate infusions or the incidence of new fragility fractures, were not systematically assessed, although these are crucial for evaluating the drug's efficacy and safety beyond the initial dose. Future research should explore these aspects to provide a more comprehensive understanding of the treatment's impacts.

To conclude, the majority are given zoledronate for indications in line with local and national guidance. Improvements can be made regarding the assessment of fracture risk, but the proportion assessed in the study is higher than other published reports. From this audit, the range of symptoms experienced and the proportion affected have been quantified. This study offers real-world prescribing data that can inform larger studies.

Furthermore, the duration and onset of symptoms have been reported. In addition, South Asian females reported a higher incidence of side effects (63%), consistent with findings from the Horizon Pivotal Fracture Trial. Future research should explore genetic or environmental factors contributing to this increased susceptibility. Future studies should focus on long-term adherence beyond 52 weeks. This will allow us to determine predictors of poor response and increased side effects.

Data Availability Statement: The data that support the findings of this study are available on request from the corresponding author.

Ethics Committee Approval: All data is anonymized and does not compromise patient confidentiality. This project protocol was registered on the Clinical Audits and Registries Management Service (CARMS) and accepted by the University Hospitals Birmingham NHS Trust Clinical Governance Team- ID: Q784389 on 10/09/2022.

Informed Consent: Written informed consent was obtained from the patients who agreed to take part in the study.

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Declaration of Interests: The authors have no conflict of interest to declare.

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