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Evaluation of pathological fractures in orthopaedic practice with emphasis on histopathology and anaesthetic challenges: a hospital-based cross-sectional study.

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Abstract

Background

Pathological fractures occur through structurally weakened bone and require coordinated orthopaedic stabilization, histopathological diagnosis, and careful anaesthetic management.

Objectives

To evaluate the clinical profile, histopathological spectrum, orthopaedic management, anaesthetic challenges, and perioperative complications among patients presenting with pathological fractures

Methods

A hospital-based descriptive cross-sectional study included 100 consecutive patients with pathological or impending pathological fractures treated at Government Medical College and Government General Hospital, Rajanna Sircilla, Telangana, India, from November 2025 to April 2026. Clinical characteristics, fracture site, histopathological diagnosis, orthopaedic treatment, anaesthetic technique, anaesthetic challenges, and perioperative complications were collected using a structured proforma and summarized using descriptive statistics.

Results

The mean age was 44.8 ± 17.6 years, and 58.0% of patients were male. Fractures followed trivial trauma in 63.0% of cases, while 21.0% occurred spontaneously and 16.0% were impending fractures. The femur was the most commonly affected bone (48.0%). Malignant lesions accounted for 65.0% of cases, with metastatic carcinoma comprising 38.0% of all diagnoses. Internal fixation was the most common surgical procedure (43.0%). General anaesthesia was used in 52.0% of patients, followed by regional anaesthesia (36.0%). Anaesthetic challenges occurred in 62.0% of patients, mainly preoperative anaemia (34.0%), cardiopulmonary comorbidities (28.0%), anticipated major blood loss (25.0%), and positioning difficulties (22.0%). Perioperative complications were reported in 29.0%, most commonly blood transfusion (18.0%), severe postoperative pain (14.0%), and intraoperative hypotension (12.0%). No intraoperative deaths occurred.

Conclusion

Malignant bone disease, particularly metastatic carcinoma, was the leading cause of pathological fractures. Histopathological confirmation guided definitive management, while the high prevalence of anaesthetic challenges and perioperative complications highlights the importance of multidisciplinary care and individualized perioperative planning.

Recommendations

Early multidisciplinary assessment, timely biopsy, optimization of anaemia, adequate blood product preparation, and structured postoperative analgesia are recommended to improve patient outcomes.

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Introduction

Pathological fracture is an important clinical entity in orthopaedic practice because the fracture is only the visible end point of an underlying skeletal disorder. The weakened bone can result from metastatic carcinoma, primary bone malignancy, plasma cell neoplasm, benign or locally aggressive bone lesions,

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infection, or metabolic bone disease. In adults, metastatic bone disease forms a major proportion of malignant skeletal involvement, and the long bones are frequently affected because of their vascularity, marrow content, and mechanical loading [1,2]. A fracture through diseased bone therefore requires a diagnostic approach that differs from ordinary traumatic fracture care.

The initial orthopaedic decision is often urgent, particularly when the patient presents with pain, inability to bear weight, deformity, or impending fracture. However, rapid fixation without understanding the underlying pathology can compromise oncological staging, biopsy tract planning, future reconstruction, and prognosis. Mirels proposed a scoring system to estimate the risk of fracture in metastatic long-bone lesions, emphasizing the importance of site, pain, lesion type, and lesion size in treatment planning [3]. Reviews on suspected malignant pathological fractures also stress that conventional trauma fixation is not always appropriate and that radiology, pathology, oncology, anaesthesia, and orthopaedics must work in sequence [4].

Histopathology is central to this sequence. Tissue diagnosis distinguishes metastatic carcinoma from primary sarcoma, myeloma, benign lesions, chronic osteomyelitis, and metabolic bone disease. This distinction changes the operative plan, the margin of resection, the need for systemic oncological work-up, and the expected survival. Computed tomography-guided biopsy and percutaneous core biopsy have shown useful diagnostic performance in musculoskeletal tumours and pathological fractures when performed within a coordinated clinical-radiological-pathological pathway [5,6]. In resource-limited settings, documenting the histopathological spectrum also helps departments plan referral pathways, implant needs, blood bank support, and rehabilitation resources.

Surgical treatment of pathological fractures is frequently palliative but technically demanding. The femur, particularly the proximal femur and shaft, is a common site requiring internal fixation, intramedullary nailing, arthroplasty, endoprosthetic reconstruction, or cement augmentation [7-9]. These procedures differ from ordinary fracture fixation because the bone is structurally abnormal, healing potential is uncertain, and the implant must often outlast the expected survival of the patient. At the same time, anaesthesia is complicated by anaemia, tumour-related physiological stress, cardiopulmonary disease, renal dysfunction, malnutrition, prior chemotherapy or radiotherapy, difficult positioning, anticipated blood loss, and cement-related haemodynamic changes during arthroplasty [10-12]. Primary malignant bone tumours and benign bone lesions with fracture also require careful functional and oncological assessment because fracture status can influence treatment intensity and outcome [13,14].

The present study was conducted to evaluate the clinicopathological profile of patients presenting with pathological fractures in orthopaedic practice, with special emphasis on histopathological diagnosis and perioperative anaesthetic challenges. The objectives were to describe demographic and fracture-related characteristics, identify the histopathological spectrum of underlying bone lesions, document orthopaedic procedures performed, analyse the type of anaesthesia administered, and assess anaesthetic challenges and perioperative complications among 100 patients managed at a tertiary care teaching hospital.

Materials and Methods

Study design

A hospital-based descriptive cross-sectional observational study with perioperative assessment was conducted. The design was selected to characterize the clinical, histopathological, orthopaedic, and anaesthetic profile of pathological fractures during a defined study period without assigning an intervention.

Study setting

The study was undertaken in the Departments of Orthopaedics, Pathology, and Anaesthesiology at Government Medical College and its attached Government General Hospital, Rajanna Sircilla, Telangana, India. The public tertiary teaching institution is located in the Sircilla–Peddur area and has approximately 500 inpatient beds. It provides emergency, outpatient, inpatient, operative, maternity, diagnostic imaging, laboratory, histopathology, anaesthesia, critical-care, and blood-support services. The hospital primarily serves urban and rural communities across the 13 mandals of Rajanna Sircilla district, with a district population of approximately 0.55 million, and also receives referrals from neighbouring districts.

Study period, population, and sampling

Patients were recruited from November 2025 to April 2026. Consecutive sampling was used, and every patient presenting during the study period who satisfied the eligibility criteria was approached for participation. The study population comprised patients with a confirmed pathological fracture or an impending pathological fracture caused by an underlying focal neoplastic, infective, benign, locally aggressive, or metabolic bone lesion.

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Eligibility criteria

Inclusion criteria were: (1) patients of either sex and any age with a radiologically diagnosed pathological or impending pathological fracture; (2) evidence of an underlying focal bone lesion; (3) histopathological confirmation from image-guided biopsy, open biopsy, or an operative specimen; (4) treatment or perioperative assessment at the study hospital during the study period; and (5) provision of informed consent by the patient or legally authorised representative. Exclusion criteria were ordinary traumatic fractures through previously normal bone, isolated osteoporotic fragility fractures without a focal lesion, stress fractures without an identifiable pathological lesion, unavailable histopathological confirmation, incomplete clinical or perioperative records, transfer before completion of assessment, and refusal to participate.

Sample size

The sample size for estimating a proportion in a cross-sectional study was calculated using $n = Z^2p(1-p)/d^2$. In the absence of a reliable local estimate for the predominant pathological-fracture category, p was set at 50% to obtain the maximum sample size; Z was 1.96 for a 95% confidence level and absolute precision (d) was 10%. Thus, $n = (1.96^2 \times 0.50 \times 0.50)/(0.10^2) = 96.04$. The minimum sample was rounded upward, and 100 consecutive eligible patients were included.

Bias

Selection bias was reduced through consecutive enrolment of all eligible cases during the defined period. Information bias was limited by using a structured proforma, predefined variable categories, routine perioperative records, and cross-checking clinical data against radiology, operative, anaesthesia, and pathology reports. Diagnostic misclassification was minimized by requiring histopathological confirmation. Data were reviewed for completeness before analysis, and no causal or comparative inference was made beyond the descriptive study objectives.

Data collection

Age, sex, mode of presentation, fracture site, symptoms, comorbid illness, radiological impression, method of tissue sampling, histopathological diagnosis, orthopaedic procedure, anaesthetic technique, perioperative concerns, and early complications were recorded. Presentation was classified as fracture after trivial trauma, spontaneous fracture, or impending pathological fracture. Comorbidities relevant to anaesthetic planning included hypertension, diabetes mellitus, cardiopulmonary disease, renal dysfunction, anaemia, nutritional compromise, electrolyte disturbance, and coagulation abnormality.

Histopathological assessment

Tissue was obtained by image-guided core biopsy, open biopsy, or operative sampling according to lesion accessibility and the planned surgical pathway. Routine histopathological reports were grouped as metastatic carcinoma, benign or locally aggressive bone lesion, primary malignant bone tumour, plasma cell neoplasm/myeloma, chronic osteomyelitis-related fracture, or metabolic bone disease-related fracture. Definitive fracture treatment was planned after tissue diagnosis whenever the clinical condition permitted [5,6].

Anaesthetic assessment

Preoperative assessment included airway evaluation, systemic examination, comorbidity review, haemoglobin, renal function, electrolytes, coagulation profile, cardiopulmonary fitness, anticipated blood loss, positioning feasibility, and postoperative monitoring requirements. The attending anaesthesiologist selected general, regional, or combined anaesthesia according to fracture location, surgical duration, physiological reserve, coagulation status, expected blood loss, pain, and positioning difficulty [10-12].

Quantitative variables

Age was analysed as a continuous variable and summarized using mean and standard deviation. For clinically interpretable presentation of age distribution, participants were additionally grouped as ≤20, 21-40, 41-60, and >60 years; these categories reflected paediatric/young, early-adult, middle-aged, and older patient groups and were used only for descriptive tabulation. Other variables were categorical and were analysed according to prespecified clinical or diagnostic categories.

Statistical analysis

Data were checked for completeness, entered into a spreadsheet, and analysed descriptively. Continuous variables were reported as mean ± standard deviation. Categorical variables were presented as frequencies and percentages. Because the study objective was descriptive and no comparison groups were prespecified, inferential hypothesis testing was not undertaken. For variables in which more than one challenge or complication could occur in the same patient, component percentages were allowed to exceed 100%.

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Ethical considerations

Ethical approval was obtained from the Institutional Ethics Committee, Government Medical College, Rajanna Sircilla, Telangana, India, before study initiation. Written informed consent was obtained from adult participants and from parents or legally authorised representatives where applicable. Participant confidentiality was maintained through coded data entry, restricted access to study records, and reporting of aggregate results. The study was conducted in accordance with the Declaration of Helsinki and applicable national ethical guidance.

Results

Participant flow

A total of 118 patients with suspected pathological or impending pathological fractures were assessed for eligibility. Eighteen were excluded: five had ordinary traumatic fractures through previously normal bone, three had isolated osteoporotic fragility fractures without a focal lesion, three lacked histopathological confirmation, four had incomplete clinical or perioperative records, and three declined participation. The remaining 100 eligible patients completed the required clinical, histopathological, orthopaedic, and perioperative assessment and were included in the final analysis (Figure 1).

The mean age was 44.8 ± 17.6 years; 38 (38.0%) participants were aged 41-60 years, and 58 (58.0%) were male. Fracture after trivial trauma occurred in 63 (63.0%), spontaneous fracture in 21 (21.0%), and impending pathological fracture in 16 (16.0%). Comorbid illness was present in 46 (46.0%). The femur was involved in 48 (48.0%), followed by the humerus in 19 (19.0%) and tibia in 12 (12.0%) (Table 1)

Figure 1: *Participant flow through the study*

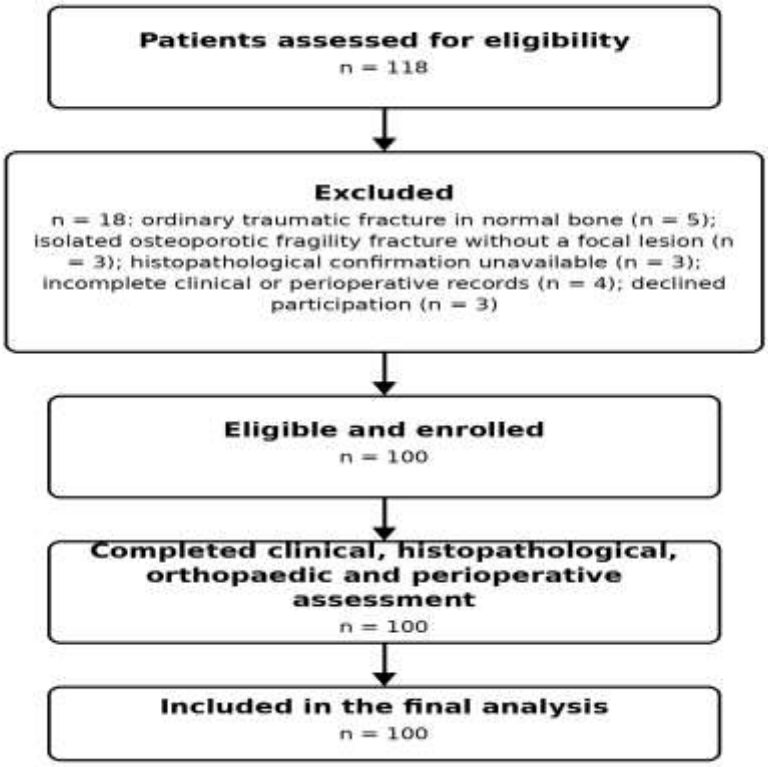

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Table 1: *Demographic, clinical, and fracture-related profile of patients*

Variable	Category	Number	Percentage
Age group	≤20 years	12	12.0
	21-40 years	26	26.0
	41-60 years	38	38.0
	>60 years	24	24.0
Sex	Male	58	58.0
	Female	42	42.0
Mode of presentation	Fracture after trivial trauma	63	63.0
	Spontaneous fracture	21	21.0
	Impending pathological fracture	16	16.0
Comorbid illness	Present	46	46.0
	Absent	54	54.0
Site of fracture	Femur	48	48.0
	Humerus	19	19.0
	Tibia	12	12.0
	Pelvis	8	8.0
	Vertebra	7	7.0
	Radius/Ulna	4	4.0
	Clavicle/Scapula	2	2.0

Note. Values are presented as n (%) unless otherwise indicated. Age was also analysed as a continuous variable (mean ± SD).

Histopathological examination identified malignant lesions in 65 (65.0%) patients: metastatic carcinoma in 38 (38.0%), primary malignant bone tumours in 15 (15.0%), and plasma cell neoplasm/myeloma in 12 (12.0%). Benign or locally aggressive lesions were found in 23 (23.0%), chronic osteomyelitis-related fractures in 7 (7.0%), and metabolic bone disease-related fractures in 5 (5.0%) (Table 2).

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Table: 2 *Histopathological diagnosis of underlying bone lesions*

Histopathological diagnosis	Number	Percentage
Metastatic carcinoma	38	38.0
Benign/locally aggressive bone lesions	23	23.0
Primary malignant bone tumours	15	15.0
Plasma cell neoplasm/Myeloma	12	12.0
Chronic osteomyelitis-related fracture	7	7.0
Metabolic bone disease-related fracture	5	5.0
Total	100	100.0

Note. Values are presented as n (%).

Internal fixation was performed in 43 (43.0%) patients, prosthetic replacement or arthroplasty in 18 (18.0%), curettage with bone grafting or cement augmentation in 16 (16.0%), tumour resection with reconstruction in 9 (9.0%), and amputation in 4 (4.0%). Biopsy followed by conservative or palliative management was used in 10 (10.0%) because of advanced disease, limited physiological reserve, or high operative risk. General anaesthesia was administered to 52 (52.0%), regional anaesthesia to 36 (36.0%), and combined general-regional anaesthesia to 12 (12.0%) (Table 3).

Table 3: *Orthopaedic management and type of anaesthesia administered*

Variable	Category	Number	Percentage
Surgical procedure	Internal fixation	43	43.0
	Prosthetic replacement/Arthroplasty	18	18.0
	Curettage with bone grafting/cement augmentation	16	16.0
	Tumour resection with reconstruction	9	9.0
	Amputation	4	4.0
	Biopsy with conservative/palliative management	10	10.0

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Variable	Category	Number	Percentage
Type of anaesthesia	General anaesthesia	52	52.0
	Regional anaesthesia	36	36.0
	Combined general and regional anaesthesia	12	12.0

Note. Values are presented as n (%).

At least one anaesthetic challenge was documented in 62 (62.0%) patients. The recorded challenges included preoperative anaemia in 34 (34.0%), cardiopulmonary comorbidity in 28 (28.0%), anticipated major blood loss in 25 (25.0%), difficult positioning due to fracture pain in 22 (22.0%), hypoalbuminaemia or poor nutritional status in 18 (18.0%), renal dysfunction in 14 (14.0%), electrolyte abnormality in 11 (11.0%), coagulation abnormality in 9 (9.0%), and anticipated difficult airway in 6 (6.0%). Perioperative complications occurred in 29 (29.0%); 18 (18.0%) required blood transfusion, 14 (14.0%) experienced severe postoperative pain requiring rescue analgesia, 12 (12.0%) developed intraoperative hypotension, 8 (8.0%) had postoperative nausea or vomiting, 4 (4.0%) had delayed recovery, and 1 (1.0%) required postoperative ventilatory support. No intraoperative death occurred (Table 4).

Table 4: *Anaesthetic challenges and perioperative complications*

Variable	Category	Number	Percentage
Anaesthetic challenges	Any anaesthetic challenge present	62	62.0
	Preoperative anaemia	34	34.0
	Cardiopulmonary comorbidity	28	28.0
	Anticipated major blood loss	25	25.0
	Difficult positioning due to fracture pain	22	22.0
	Hypoalbuminaemia/poor nutritional status	18	18.0
	Renal dysfunction	14	14.0
	Electrolyte abnormality	11	11.0
	Coagulation abnormality	9	9.0
	Anticipated difficult airway	6	6.0
Perioperative complications	Any perioperative complication	29	29.0

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Variable	Category	Number	Percentage
	Blood transfusion requirement	18	18.0
	Postoperative severe pain requiring rescue analgesia	14	14.0
	Intraoperative hypotension	12	12.0
	Postoperative nausea/vomiting	8	8.0
	Delayed recovery from anaesthesia	4	4.0
	Postoperative ventilatory support	1	1.0
	Intraoperative mortality	0	0.0

Note. Values are presented as n (%). Individual anaesthetic challenges and perioperative complications were not mutually exclusive; therefore, component percentages may total more than 100%.

Taken together, 65.0% of fractures were associated with malignant pathology, 62.0% of patients had at least one anaesthetic challenge, and 29.0% experienced an early perioperative complication. These findings demonstrate that pathological-fracture management requires coordinated diagnostic, operative, anaesthetic, transfusion, and postoperative planning.

Discussion

The principal findings were that fracture after trivial trauma was the presenting event in 63.0% of patients, the femur was affected in 48.0%, and malignant disease accounted for 65.0% of the histopathological diagnoses. Metastatic carcinoma alone represented 38.0%, while primary malignant bone tumours and plasma cell neoplasms accounted for 15.0% and 12.0%, respectively. Internal fixation was used in 43.0%, at least one anaesthetic challenge was present in 62.0%, and early perioperative complications occurred in 29.0%. The most frequent perioperative concerns were anaemia (34.0%), cardiopulmonary comorbidity (28.0%), anticipated major blood loss (25.0%), and painful positioning (22.0%). These results show that a pathological fracture is not merely a mechanical failure of bone; it is a combined marker of lesion biology, systemic disease burden, and perioperative vulnerability.

The predominance of femoral involvement (48.0%), followed by the humerus (19.0%) and tibia (12.0%), is consistent with previous literature emphasizing the susceptibility of mechanically loaded long bones, particularly the proximal femur, to metastatic destruction and fracture [1,2,7-9]. High marrow vascularity facilitates tumour-cell seeding, while weight bearing and bending forces increase the probability that an osteolytic or structurally disorganized lesion will fail. The 63.0% frequency of trivial-trauma presentation is therefore clinically plausible and reinforces the need to investigate low-energy fractures for an underlying lesion rather than managing them as routine trauma alone. The lower proportions of pelvic (8.0%) and vertebral (7.0%) fractures may partly reflect referral patterns, because axial skeletal lesions are often managed primarily by oncology, spine, or interventional services rather than general orthopaedic trauma units.

Histopathology established a heterogeneous disease spectrum: metastatic carcinoma in 38.0%, benign or locally aggressive lesions in 23.0%, primary malignant tumours in 15.0%, myeloma in 12.0%, chronic osteomyelitis in 7.0%, and metabolic bone disease in 5.0%. The predominance of malignant pathology agrees with reviews describing metastatic disease as a major cause of pathological fractures in adults [2,4].

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Nevertheless, the substantial benign or locally aggressive component in the present cohort reflects inclusion of all eligible age groups and all focal pathological lesions rather than restriction to patients with known cancer. This mixed spectrum explains why tissue diagnosis was essential: metastatic carcinoma, sarcoma, myeloma, infection, and benign aggressive lesions require different biopsy pathways, resection margins, fixation strategies, systemic investigations, and prognostic counselling. The diagnostic role observed in this study is supported by Stokes et al. and Crenn et al., who reported that appropriately planned image-guided or core biopsy can provide reliable diagnosis in pathological fractures and primary bone tumours [5,6].

The distribution of orthopaedic treatment also reflected lesion biology and patient fitness. Internal fixation was the commonest procedure (43.0%), followed by arthroplasty (18.0%), curettage with grafting or cement augmentation (16.0%), and tumour resection with reconstruction (9.0%). Previous studies of metastatic femoral fractures have similarly described intramedullary fixation and endoprosthetic reconstruction as principal options, selected according to lesion location, remaining bone stock, expected survival, and implant durability [7-9]. In the present study, curettage-based procedures were more applicable to benign or locally aggressive lesions, consistent with the lesion-specific approach reported for benign tumour-related fractures [14]. Conversely, 10.0% received biopsy with conservative or palliative care, which likely reflects advanced disease, limited functional benefit from major surgery, or inadequate physiological reserve. Thus, the observed procedure profile represents individualized decision-making rather than a single standardized fixation strategy.

Anaesthetic challenges affected 62.0% of patients. Anaemia (34.0%), cardiopulmonary comorbidity (28.0%), anticipated major blood loss (25.0%), poor nutritional status (18.0%), renal dysfunction (14.0%), electrolyte abnormality (11.0%), and coagulation abnormality (9.0%) indicate a substantial burden of systemic illness. Anderson et al. similarly emphasized that orthopaedic oncological surgery is complicated by variable operative duration, major blood loss, previous anticancer therapy, cardiopulmonary impairment, renal dysfunction, and difficult positioning [10]. The high frequency in the present cohort may be explained by malignant disease in 65.0%, painful long-bone fractures, delayed presentation, chronic inflammation, marrow involvement, malnutrition, and treatment-related physiological depletion. Positioning difficulty in 22.0% is particularly relevant because regional blocks, neuraxial procedures, airway management, and surgical positioning may all aggravate pain or risk further displacement. Early perioperative complications occurred in 29.0%, with transfusion in 18.0%, severe postoperative pain in 14.0%, and intraoperative hypotension in 12.0%. Janssen et al. specifically evaluated allogeneic transfusion in surgery for long-bone metastatic fractures, supporting the clinical importance of haemoglobin status and blood-product exposure in this population [11]. The transfusion rate in the present study is compatible with the combination of preoperative anaemia, tumour vascularity, extensive dissection, intramedullary instrumentation, and arthroplasty. Hypotension may have resulted from anaesthetic induction, blood loss, reduced cardiovascular reserve, or cement-associated haemodynamic effects; the need for vigilance during cemented procedures is supported by haemodynamic studies of hip arthroplasty [12]. Severe postoperative pain despite surgery indicates the need for scheduled multimodal analgesia and regional techniques where feasible. No intraoperative mortality occurred, which may reflect preoperative optimization, selective avoidance of major surgery in high-risk patients, and coordinated multidisciplinary care. Direct numerical comparison with previous studies remains limited because published cohorts differ in tumour type, fracture site, operative procedure, and duration of follow-up.

Generalizability

The findings are most applicable to public tertiary teaching hospitals that manage a mixed spectrum of neoplastic, infective, benign, and metabolic pathological fractures with access to orthopaedics, pathology, radiology, anaesthesia, blood support, and referral oncology services. The consecutive hospital-based sample reflects routine clinical workload; however, lesion distribution and treatment patterns may differ in dedicated cancer centres, paediatric hospitals, spine units, or facilities without onsite histopathology.

Conclusion

In this hospital-based cross-sectional study, malignant lesions caused 65.0% of pathological fractures, metastatic carcinoma was the single largest diagnosis (38.0%), and the femur was the predominant site (48.0%). Internal fixation was performed in 43.0%. Anaesthetic challenges were documented in 62.0%, and perioperative complications occurred in 29.0%, principally transfusion requirement, severe postoperative pain, and hypotension. Histopathological confirmation, early anaesthetic assessment, correction of reversible abnormalities, blood preparedness, individualized reconstruction, and structured postoperative analgesia should therefore be integrated into a multidisciplinary pathway for pathological-fracture care.

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Limitations

The single-centre cross-sectional design limits causal inference and may not represent the disease spectrum of dedicated oncology or paediatric centres. Although early perioperative complications were recorded, long-term survival, recurrence, implant durability, union, functional recovery, and oncological response were not evaluated. The study did not stratify outcomes by tumour stage, primary cancer, fracture location within each bone, surgical complexity, or anaesthetic technique. Multivariable analysis was not performed, and patient-reported outcomes and cost data were unavailable.

Recommendations

Patients with suspected pathological fractures should undergo early multidisciplinary assessment involving orthopaedics, pathology, radiology, anaesthesia, and oncology. Tissue diagnosis should be obtained before definitive fixation whenever feasible. Preoperative optimization should include correction of anaemia, review of renal and cardiopulmonary status, electrolyte stabilization, and blood product preparedness. Anaesthetic plans should consider positioning difficulty, anticipated blood loss, cement-related haemodynamic risk, postoperative analgesia, and need for higher-dependency monitoring. Hospitals managing these cases should maintain a local protocol for biopsy planning, implant selection, transfusion preparedness, and postoperative rehabilitation. A simple checklist can help standardize preoperative assessment and team communication.

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Abbreviations

BCIS-bone cement implantation syndrome;

CT-computed tomography;

MRI-magnetic resonance imaging.

Source of funding

The study had no funding.

Conflict of interest

The authors declare no conflict of interest.

Author contributions

KA-Concept and design of the study, results interpretation, review of literature and preparing first draft of manuscript. Statistical analysis and interpretation, revision of manuscript**. AS** - Design of the study, results interpretation, review of literature and preparing first draft of manuscript, revision of manuscript.**RC**- design of the study, results interpretation, review of literature and preparing first draft of manuscript. Statistical analysis and interpretation, revision of manuscript

Data availability

Data Available

Author Biography

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