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Proximal femoral multiple myeloma pathological fractures, impending and actual fractures – a patient survival study

Oded Hershkovich[1,2*†], Mojahed Sakhnini[1†], Gal Barkay[1], Boaz Liberman[1], Alon Friedlander[1] and Raphael Lotan[2]

Abstract

Introduction The femur is a common site for Multiple Myeloma (MM) involvement. This study explores the impact of preventive surgery for anticipated femoral pathological fractures (IFF), based on Mirels classification, versus treatment of pathological femur fracture (PFF) on MM patient mortality and morbidity.

Methods Retrospective cohort of 33 patients undergoing surgery due to femoral MM involvement (2004–2015), 18 patients with PFF, 15 patients with IFF, followed up until deceased or to July 2016. Demographic data, oncological, pathological, radiation, surgical reports, outpatient clinical records, and imaging studies were studied. Exclusion criteria included patients who had surgery at other medical centers.

Results The mean age was 70.4 ± 13.6 and 62.6 ± 12.2 years ($p = 0.1$) in the PFF and the IFF cohorts, respectively, primarily women (55.6% and 46.7%, respectively). The average Mirels' score was 10.4 ± 1.2. Post-operative complications were observed in 25% of patients, with no difference between IFF & PFF. We did not find a difference in mortality between IFF and PFF cohorts ($p = 0.59$).

Conclusion The femur is commonly involved in MM. This study found that actual fractures, compared to imminent fractures, do not affect MM morbidity or mortality. Our study shows that proximal femoral MM behaves differently from proximal femoral metastatic disease regarding the impact of surgery on life span. Due to the fracture healing potential of MM, an IFF can probably be treated initially conservatively unless it progresses to an actual fracture needing surgery. Future, more extensive studies are required before revolutionizing the proximal femoral Multiple Myeloma-related involvement treatment paradigm.

Highlights

The femur is a common site for Multiple Myeloma (MM) involvement. Earlier studies did not assess the impact of preventive surgery for anticipated femoral pathological fractures (IFF) to the treatment of pathological femur fracture (PFF) on MM patient mortality and morbidity. In this retrospective cohort of patients undergoing surgery due to femoral MM involvement, we found that actual fractures, compared to imminent fractures, do not affect morbidity or mortality. Our study shows that proximal femoral Multiple Myeloma behaves differently from proximal femoral

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metastatic disease regarding the impact of surgery on life span. Due to the fracture healing potential of Multiple Myeloma, an IFF can probably be treated initially conservatively unless it progresses to an actual fracture needing surgery. Future, more extensive studies are required before revolutionizing the proximal femoral Multiple Myeloma -related involvement treatment paradigm.

Keywords Femur, Multiple Myeloma, Metastases, Survival

Introduction

The skeleton ranks as the third most frequent site for metastatic involvement, following the lung and liver. Prostate, breast, lung, renal, and thyroid carcinomas constitute 80% of all skeletal metastases, with the femur being the most commonly affected long bone [1, 2]. Multiple Myeloma (MM) is a bone marrow plasma cell infiltrating malignant tumour that causes widespread osseous lytic lesions leading to pathologic fractures. The median age at the onset of Multiple Myeloma is 69 years, and approximately 63% of patients diagnosed with Multiple Myeloma are older than 65. Multiple Myeloma is most prevalent in people older than 65 in industrialized countries such as Australasia, North America, and Western Europe [3]. Multiple Myeloma osseous involvement encompasses 80–90% of patients; the axial skeleton, particularly the spine, and the proximal long bones are most often affected, but any bone can be involved. Amongst the most frequently involved locations are the spine (49%), the pelvis (34%), the humeri (22%,) and the femora (13%). Multiple Myeloma osteolytic involvement causes local bone pain in 80% of the patients and mechanical destabilization, leading to pathological fractures; 60% of patients develop pathological fractures throughout the disease [4–6]. With improved oncological treatment, prolonged patient survival leads to an increased prevalence of osseous disease and eventually to impending or pathological fractures, as classified by Mirels et al. [7]. Once this complication occurs, it can contribute to the quality of life deterioration and possibly reduce survival [8, 9]. In a population-based retrospective study, Multiple Myeloma patients had a ninefold increased risk of fractures [10].

There is increased attention on the adequate management of patients with proximal femur metastases due to patients' increasing life expectancy and the need to maintain good function and quality of life [8]. When dealing with impending or actual pathologic fractures, treatment should aim to control pain, ensure stable and secure fixation, and enable immediate weight-bearing, ideally lasting longer than the patient's remaining lifespan. The most commonly utilized classification system for impending fracture risk assessment is the Mirels' classification. Mirels' classification [7] for impending long bone pathological fractures is a system used to assess the risk of a bone fracture in individuals with metastatic bone diseases, but without a specific Multiple Myeloma classification system, it is still the most commonly used for Multiple Myeloma long bone involvement. The classification is based on five criteria: the long bone involved, the metastatic lesion's location, density or matrix, and pain. Criteria are evaluated on a scale of 1 to 3, where higher values signify an elevated fracture risk. The overall fracture risk is then determined by summing the scores for each criterion. Although Mirels' classification was used for metastatic carcinomas, it is the only tool available for impending fracture assessment, thus, has a place in assessing Multiple Myeloma proximal femoral involvement.

In elderly individuals, femoral fractures are a well-documented cause of death and illness, especially with conservative treatment. This is due to immobility-related complications such as pneumonia, deep vein thrombosis, and urinary tract infections [11, 12]. Patients with metastatic carcinoma exhibit similar levels of metabolic vulnerability and susceptibility to infections [13, 14]. The effects of metastatic femoral fractures have been researched, and preventive surgery is recommended to mitigate potential complications from fractures [15–17]. Earlier studies have shown that preventive fixation of impending pathological fractures leads to improved survival rates compared to treating acute pathological fractures [18]. However, prophylactic fixation also comes with disadvantages, including an increased risk of venous thromboembolic events and deep vein thrombosis [19]. A recent population-based study showed a significantly increased mortality in Multiple Myeloma-related proximal femoral fractures compared to fractures of other sites, spine, pelvis, ribs and humerus [20]. Age older than 70 was also found as a mortality risk factor.

Despite the high prevalence of Multiple Myeloma, the high percentage of osseous disease, specifically femoral involvement, and the increased risk of mortality in these fractures, no studies are looking into the role of preventive surgery for impending fractures in Multiple Myeloma patients, in contrast to the numerous studies examining metastatic femoral involvement. Multiple Myeloma bone involvement and pathophysiology are very different from the metastatic mechanism affecting the bones. In Multiple Myeloma, the balance between osteoblasts and

osteoclasts becomes disrupted, resulting in bone resorption. However, when the disease is adequately controlled, the balance is restored, allowing the formation of new bone and fracture healing [21]. Concerning pathological fracture healing potential, Multiple Myeloma differs from metastatic pathological fractures [22]. In a recent JAAOS Clinical Practice Guideline Summary [23], the most prominent conclusion was the paucity of high-quality studies examining patient treatment-related outcomes. Moreover, Multiple Myeloma was not distinguished from metastatic involvement of the femur. However, Multiple Myeloma is different from Metastatic carcinomas regarding cell origin, disease characteristics, treatment options and reaction to treatment. A literature search did not find a single study examining the proximal femoral Multiple Myeloma involvement course and the implications of preventive surgery for impending fractures. Despite Multiple Myeloma being different from metastatic carcinomas of the femur, previous studies bundled patients of both entities, maybe acting as a confounder leading to over-aggressive treatment of Multiple Myeloma patients.

Since Multiple Myeloma differs from metastatic carcinomas by cell origin, treatments and survival should be assessed separately from metastatic femoral disease. Since this is the first study ever assessing the impact of preventive treatment of Multiple Myeloma proximal femoral disease, we did not know whether preventive surgery improves survival or does not impact it. This study evaluates the impact of preventive surgery for impending MM-related femoral pathological fracture versus treating an actual pathological fracture on patient mortality and morbidity.

Methods

Records of all patients who had surgery for a femoral lesion related to Multiple Myeloma between October 2004 and May 2015 were reviewed. Surgical indications were impending fracture, Mirels score above 7 points, or a pathological femoral fracture. For each patient, a multidisciplinary team, a hematologist and an orthopedic surgeon assessed the patient's data and dictated treatment. Surgical treatment was dictated by the area of involvement and extent of disease; femoral head involvement was treated by hemiarthroplasty or total hip replacement, while pertrochanteric involvement was treated by osteosynthesis with poly-methyl-methacrylate for improved structural integrity. Patients were followed up until they were deceased or up to July 2016. Demographic information, oncologic and pathology reports, radiation records, surgical documentation, outpatient clinical records, and imaging studies were gathered and analyzed. Pre and postoperative imaging studies collected were assessed, including X-rays, CT, bone scans, and PET-CT. The date of death was confirmed with the Ministry of the Interior up to July 2016. Treatment strategies prior to proximal femoral myeloma involvement, such as steroid and bisphosphonate treatments, were unavailable.

Exclusion criteria included patients who had surgery at other medical centers. Multiple Myeloma osseous lesions involving the femoral shaft and distal femur were excluded since this study aimed to evaluate only proximal femoral involvement. There were no patients lost to follow-up. There were no femoral solitary plasmacytoma cases in the cohort. Patients with multiple femoral lesions were not included in order to isolate the effect of proximal femoral pathological fractures on survival.

Descriptive statistics were used to evaluate study population, complication rates, and survival. Categorical data are presented as frequency (percent). Continuous-data was expressed as mean and standard deviation. Differences in characteristics between anatomical sites and surgical modalities were analyzed using ANOVA, followed by the Tukey–Kramer test for multiple comparisons. The Fisher-exact test was utilized to compare 30-day systemic and local complication rates among different surgical strategies.

Post-surgery follow-up time was defined as the time from surgery to either death or the end of follow-up (censuring). Kaplan–Meier survival curves were used for plot-ting time from surgery to either censuring or mortality. Survival curves were com-pared using the log-rank test (Mantle-Cox test). P-value was considered statistically significant when 0.05 or less. P-values reported were always two-sided. The IBM SPSS 23.0 software was used for the statistical analysis.

This study did not receive funding. The Sheba Medical Center, Tel Hashomer, affiliated with the School of Medicine, Tel Aviv, Israel, Institutional Review Board approved this study. The same IRB waived the need to obtain informed consent due to the study's retrospective nature. This study was conducted according to principles outlined in the Declaration of Helsinki. Our complete data is available under confidentiality restrictions.

Results

This study included 33 patients who underwent surgery due to Multiple myeloma-related proximal femoral disease, 18 patients suffering from a proximal femoral pathological fracture (PFF), and 15 patients with impending femoral fracture (IFF) (Table 1). The mean age of the patients in the PFF cohort was 70.4 ± 13.6, and of the IFF, 62.6 ± 12.2 years ($p = 0.10$) (Table 1). 56.6% of the PFF were women, and 46.7% of the IFF cohort ($p = 0.10$). The average Mirels' score was 10.4 ± 1.2, indicating an impending fracture requiring surgical stabilization or replacement. The mean time from diagnosis to

Table 1 Patient characteristics with Multiple Myeloma by pathological or impend-ing fractures

	Pathological fracture	Impending fracture	*p*-value
Age	70.4 ± 13.6	62.6 ± 12.2	0.10
Gender, Females	55.6%	46.7%	0.10
Mirels	––	10.4 ± 1.2	
Karnofsky score	65.3 ± 15.7	65.3 ± 13	0.42
Lesion Location:			
Femoral head	0%	13.3%	0.11
Femoral neck	77.8%	26.7%	0.003
Pertrochanteric	11.1%	60%	0.003
Subtrochanteric	11.1%	0%	0.18
Multiple Osseous lesions	2.1 ± 1.3	1.8 ± 1.1	0.46
Time from diagnosis to surgery (years)	3 ± 4	4.1 ± 3.4	0.42
Post-op survival (days)	897.1 ± 826.8	1037.3 ± 630.9	0.59

surgical intervention was 3 ± 4 years for the PFF cohort and 4.1 ± 3.4 for the IFF ($p = 0.42$). The cohort's similar length of multiple myeloma disease duration suggests a similar clinical stage. Only one patient had a multiple myeloma proximal femoral pathological fracture as a presenting symptom; all other patients were diagnosed and treated prior to the proximal femoral involvement. Previous multiple myeloma treatment protocol data was unavailable.

Multiple Myeloma Femoral lesion locations

The most common femoral Multiple myeloma-related involvement in the PFF was the femoral neck, 77.8%, while in the IFF cohort, the most common involvement was pertrochanteric, 60% ($p = 0.003$)(Table 1). Time from Multiple Myeloma diagnosis to surgery was three years for the PFF cohort and 4.1 years for the IFF cohort, but the difference was not statistically significant ($p = 0.242$). At the time of surgery, multiple osseous lesions were apparent in at least two sights on average per patient in both cohorts ($p = 0.46$). Patients with multiple osseous lesions in the same femur were excluded to isolate proximal femoral MM involvement's effect on survival.

Postoperative complications

Seventy-five percent of patients underwent surgery without postoperative complications and were discharged home or to a rehabilitation institution. No statistically significant difference was found between IFF and PFF regarding postoperative complications (Table 2). The most common complication for IFF was surgical site infection (9.1%) and pneumonia for the PFF (9.1%). Only one patient in the IFF cohort required revision surgery. All surgical site infections (SSI) were treated with antibiotics, not requiring revision surgery.

Table 2 Postoperative Complications by IFF/PFF

	IFF	PFF (%)	Total (%)	*p*-value
DVT	4.5	4.5	4.5	1
SSI	9.1	0	4.5	0.15
Pneumonia	4.5	9.1	6.8	0.55
MI	4.5	0	2.3	0.31
PE	0	4.5	2.3	0.31
Periprosthetic fracture	4.5	0	2.3	0.31
Revision survey	4.5	0	2.3	0.31
No complications	68.2	81.8	75	0.30

Mortality

Minimal postoperative survival for the IFF and PFF patients was 71 days; none died in the immediate postoperative 30 days. Average postoperative survival was longer for the IFF compared to the PFF cohorts, 1037.3 ± 630.9 and 897.1 ± 826.8 days, respectively ($p = 0.59$) (Table 1, Fig. 1). The Kaplan–Meier survival analysis indicated no significant statistical difference in survival between actual pathological proximal femoral fractures and imminent fractures (Fig. 1).

Discussion

Proximal femoral involvement by metastatic disease and Multiple Myeloma is relatively common, and the incidence rises with better oncologic and hematologic treatments [24, 25]. The impact of a pathological femoral fracture on patient survival compared to preventive surgery for impending fractures has been studied [26, 27]. Philipp et al. [27] and Owen et al. [17] found greater overall survival among patients undergoing prophylactic stabilization of metastatic femoral lesions than those with

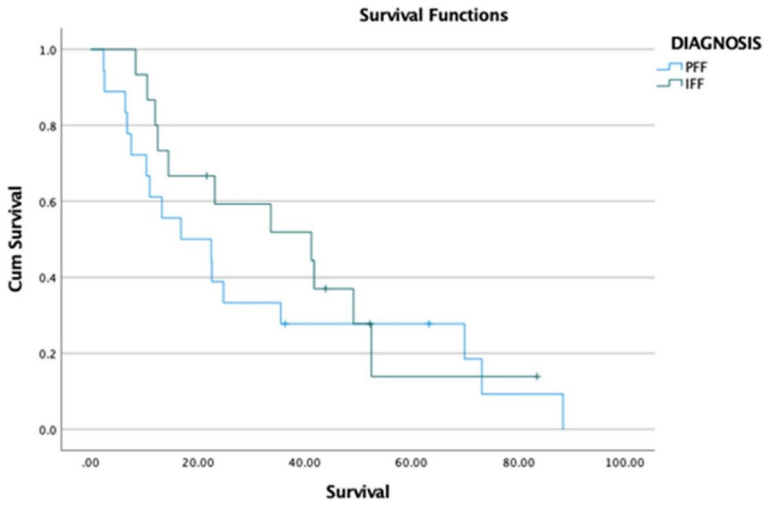

Fig. 1 Kaplan-Meyer survival plot according to the actual or impending proximal femoral fractures

fixation of complete pathologic fractures, while Aneja et al. [19] found a higher complication rate in the prophylactic stabilization patients. These studies included carcinomatous metastases as well as Multiple Myeloma. Piccioli [28] found breast tumours responsible for 29% of femoral metastasis, followed by multiple Myeloma 20%, prostate 15% and lung 10%. Most femoral metastases favour the proximal areas [29, 30], with 71% of all metastases located in the neck and trochanteric area, regardless of tumour origin.

Currently, there is no available data regarding the impact of Multiple Myeloma proximal femoral involvement on the timing of surgery, patient outcomes and survival despite the high prevalence of Multiple Myeloma, the high percentage of osseous disease, specifically femoral involvement, and the increased risk of mortality in these fractures, in contrast to the numerous studies examining metastatic femoral involvement. In a recent JAAOS Clinical Practice Guideline Summary [23], the most prominent conclusion was the paucity of high-quality studies examining patient treatment-related outcomes, specifically regarding Multiple Myeloma. Moreover, Multiple Myeloma was not distinguished from metastatic involvement of the femur. The Multiple Myeloma subcohorts usually constitute the minority of the patients, ranging from 9.5% to 15% of the cohort Treatment of pathologic fractures of the proximal femur [8, 31]. However, Multiple Myeloma differs from Metastatic carcinomas regarding cell origin, disease characteristics, treatment options, reaction to treatment and fracture healing potential. A literature search did not find a single study examining the proximal femoral Multiple Myeloma involvement course and the implications of preventive surgery for impending fractures. Despite Multiple Myeloma being different from metastatic carcinomas of the femur, previous studies bundled patients of both entities, maybe acting as a confounder leading to over-aggressive treatment of Multiple Myeloma patients.

In our Multiple Myeloma cohort, the most common area of involvement was the femoral neck and pertrochanteric area, accounting for 88.9% in the PFF group and 86.7% in the IFF group (Table 1). Still, IFF had a higher incidence of pertrochanteric involvement, while the PFF tended to involve the femoral neck. Our cohort did not include lesions involving the femoral midshaft or the distal femur. Orthopedic surgeons consider the proximal femur a significant weight-bearing area; the specific location of metastatic disease or Multiple Myeloma impacts surgical technique but not survival.

Postoperative complications can be severe for multiple myeloma patients and impact their quality of life, resulting in high morbidity and delayed rehabilitation in patients with impeded survival. In our study, only 75% of the patients had an uneventful recovery, while 25% had at least one complication; this can be attributed to the systemic hematological burden and patient fragility. We did not find a statistically significant difference in morbidity following Multiple Myeloma-related pathological fractures compared to an impending Multiple myeloma-related femoral fracture (Table 2). However, the perioperative complication rate was relatively high, with 25% of the patients.

During the last two decades, survival rates of Multiple Myeloma patients have improved. Before 2000, the median overall survival of Multiple Myeloma was closer to 30 months. A long-term follow-up analysis, median follow-up of 67 months, of 1000 patients with newly diagnosed Multiple Myeloma treated between 2007 and

2016 with a combination of lenalidomide, bortezomib, and dexamethasone induction therapy reported a median overall survival of 126.6 months. Despite the improved survival rates for newly diagnosed Multiple Myeloma, approximately 20% have substantially worse outcomes [3]. There was no perioperative mortality; the earliest mortality was recorded 71 days following surgery in the PFF and 254 days in the IFF. Overall survival of proximal femoral multiple myeloma-related fractures was 960.8 ± 736.4 days. We did not find a statistically significant difference between IFF and PFF survival, $p = 0.59$ (Table 1). The published expected 5-year survival of multiple myeloma patients in our cohort's age group is around 50% [32, 33]. In our study, Multiple myeloma-related proximal femoral involvement in the IFF and PFF cohorts occurred 3–4 years from Multiple Myeloma diagnosis; when combining the time from diagnosis to fracture and postoperative survival, patients in our cohort lived to the reported expected life span. We did not find a statistically significant effect of preventive surgery for impending Multiple Myeloma-related proximal femoral involvement on patients' perioperative survival or life span compared to surgery for actual pathological fractures. The average survival difference between the cohorts was 140.2 days in favor of the IFF cohort, 4.7 months, from an overall survival average of 32 months following treatment. These results suggest that Multiple Myeloma patients with proximal femoral involvement may be treated conservatively, by radiation treatment or systemically, prior to surgery without compromising survival while avoiding a relatively high perioperative complication rate. However, due to the small sample size, further large-scale studies are needed to support our findings.

A previous large-scale population-based epidemiological study discovered that Multiple Myeloma patients with fractures have a twofold increased risk of death compared to those without fractures, demonstrating the significant impact of fractures on patients with Multiple Myeloma, a higher risk than previously reported in clinical cohorts [20]. These results were further validated when it was observed that Multiple Myeloma patients who experienced fractures during the initial months of the disease had poorer survival rates compared to those without fractures. These findings align partially with observations in the general population, where fractures, particularly osteoporotic ones, are linked to an increased risk of death, although not to the same degree as seen in Multiple Myeloma patients. Fractures occurring after Multiple Myeloma diagnoses may indicate an aggressive relapse. The main limitation of this study was the lack of clinical data on these patients. Our study included patients that, on average, survived 3–4 years following Multiple Myeloma and developed proximal femoral involvement as a late sequela of the disease, a high-risk cohort. However, still, there was no difference in survival time between impending and actual pathological proximal femoral fractures.

To the best of our knowledge, This is the first study focusing on the effect of Multiple myeloma-related proximal femoral involvement on patient morbidity and mortality, in contrast to the existing studies that did not differentiate Multiple Myeloma patients. MM proximal femoral involvement is currently considered the same as femoral metastatic disease, typically undergoing preventive surgery. Our study is the first to look specifically at MM proximal femoral involvement, suggesting that hematologists could treat eminent fractures systemically and actual fracture prevention does not impede patient survival, unlike in metastatic femoral disease. According to our results, Proximal femoral Multiple Myeloma is not the same as proximal femoral carcinomatous metastasis. Compared to metastatic PFF or IFF, which affects mortality, proximal femoral Multiple Myeloma does not affect mortality, and preventive IFF surgery may be unnecessary, probably due to the Multiple Myeloma fracture healing potential. In Multiple Myeloma-related IFF cases, treatment may include reduced weight-bearing, hematologic treatment and follow-up since these impending fractures can potentially heal with Multiple Myeloma treatments. Patients who progress under treatment to actual fractures will require surgery, but the delay does not seem to affect morbidity or mortality. This study did not look at the Multiple myeloma treatment protocols, disease progression, and its systemic effects but instead examined the influence of proximal femoral involvement treatment on patient survival. Future studies must assess Multiple Myeloma osseous involvement as a unique disease, separating it from metastatic carcinomatous disease.

The study's limitations encompass its retrospective design and potential selection bias in the impending pathological fracture group, as the patient's subjective pain is evaluated by the Mirels classification as well as the location of the osseous lesion and may lead to surgery regardless of the lesion's size. This study does not evaluate MM treatment protocols; data regarding previous treatment regimens or post-proximal femoral MM involvement treatment strategies are unavailable and beyond this study's scope. Since both cohorts were treated at the same hematology department, we speculate that treatment variability was low and patients were treated similarly to the disease stage. This study did not measure pain scores, quality of life or function, which might differ between the groups. Future studies should include cytogenetics and staging data to decrease the

heterogeneity effects on the study. Another limitation is the study's sample size, which requires further extensive studies before revolutionizing the proximal femoral Multiple myeloma-related involvement treatment paradigm.

In conclusion, the femur is commonly involved in Multiple Myeloma. This study found that actual fractures, compared to imminent fractures, do not affect Multiple Myeloma morbidity or mortality. Our study shows that proximal femoral Multiple Myeloma behaves differently from proximal femoral metastatic disease regarding the impact of surgery on life span. Due to the fracture healing potential of Multiple Myeloma, an IFF can probably be treated initially conservatively unless it progresses to an actual fracture needing surgery. Future, more extensive studies are required before revolutionizing the proximal femoral Multiple Myeloma -related involvement treatment paradigm.

Authors' contributions

OH—Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Resources, Supervision, Validation, Visualization, Writing—original draft, Writing—review & editing. MS—Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Resources, Supervision, Validation, Visualization, Writing—original draft, Writing—review & editing. GB—Data curation, Formal analysis, Investigation, Project administration, Validation, Writing—original draft, Writing—review & editing. BL—Data curation, Formal analysis, Investigation, Project administration, Validation, Writing—original draft, Writing—review & editing AF—Conceptualization, Investigation, Methodology, Supervision, Validation, Writing—original draft, Writing—review & editing. RL—Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Resources, Supervision, Validation, Visualization, Writing—original draft, Writing—review & editing.

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Availability of data and materials

All complete data are available under confidentiality restrictions. Any person who wishes to content this manuscript data should contact the corresponding author: Oded Hershkovich; mailing address: Ha-Lokhamim St 62, Holon, 5,822,012; Phone: +972–3-5,028,383; Fax: +972–3-5028774; Email: oded.hershkovich@gmail.com; odedh@WMC.gov.il.

Declarations

Ethics approval and consent to participate

The study was conducted in accordance with the Declaration of Helsinki, and approved by the Sheba Medical Center, Tel Hashomer, affiliated to the Sackler School of Medicine, Tel Aviv, Israel.

Consent for publication

No informed consent was required for this study.

Competing interests

The authors declare no competing interests.

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