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Differential survival among individuals with active and healed periosteal new bone formation

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ABSTRACT

Periosteal new bone formation is frequently used in paleopathological and paleoepidemiological studies to diagnose particular diseases or to assess non-specific stress in past populations. Many researchers distinguish between active (woven or unremodeled) and healed (sclerotic or remodeled) periosteal lesions during data collection, but few published studies maintain a distinction between these two activity categories in analysis or interpretation. Though it has been suggested that healed periosteal lesions might indicate relatively good health and enhanced survivorship, no study has explicitly examined this possible relationship in a large skeletal sample that includes both children and adults. This study examines the relationship between periosteal lesion activity (active vs. healed) and survival using a sample of 538 individuals from several medieval London cemeteries, which in combination span the period 1120–1538. The results of Kaplan–Meier survival analysis indicate that healed periosteal lesions are associated with survival advantages compared to both those with active lesions and those without any lesions at all. These results suggest that active periosteal lesions might most closely reflect high frailty and bioarchaeological studies should focus on the distinction between the presence or absence of *healing* rather than merely on the presence of periosteal lesions irrespective of their activity.

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1. Introduction

Periosteal new bone formation (i.e. periosteal lesions) is a proliferative skeletal lesion that occurs in response to stimuli that tear, stretch, compress or otherwise traumatize the periosteum, and as a result of local or systemic infection or inflammation associated with a variety of factors (Larsen, 1997; Ortner, 2003; Weston, 2008). Though typically viewed by bioarchaeologists as a marker of traumatic injury or an infection, periosteal new bone formation can occur as a result of a nutritional imbalance (Huss-Ashmore et al., 1982; Paine and Brenton, 2006); for example, localized hemorrhages resulting from vitamin C deficiency can lead to the proliferation of new bone (Geber and Murphy, 2012; Roberts and Manchester, 2005). Periosteal lesions are also associated with neoplastic, metabolic, congenital, and genetic diseases (Chen et al., 2012). New bone formation ultimately occurs because of the activity of osteoblasts, and disease, injury, or other factors that result in an increase in vascular permeability and edema can create conditions that are favorable to osteoblast activity (e.g. providing the material necessary for bone matrix production) (Ragsdale and Lehmer, 2012). Damage to the periosteum can result in blood seeping from associated blood vessels and subsequent hematoma formation, and this triggers inflammatory responses that can lead to the formation of new bone (Bastian et al., 2011). Though inflammation – which is the body's response to physical or chemical damage, invasion by pathogens, and other harmful stimuli – can interfere with bone formation by downregulating osteoblast activity and promote bone resorption by increasing osteoclast activity, some pro-inflammatory mediators do promote new bone formation (Thomas and Puleo, 2011). For example, the pro-inflammatory cytokines IL-1β and TNF-α and β can stimulate osteoblastic proliferation and the production of mineralized bone matrix (Frost et al., 1997; Lange et al., 2010). Some pro-inflammatory mediators cause vasodilation (DeFranco et al., 2007), and increased blood flow at the site of inflammation can result in periosteal hyperplasia and thus new bone formation (Walton and Rothwell, 1983). In addition to being influenced by inflammatory factors, the formation of periosteal new bone is affected by hormones and other signaling molecules (Dimitriou et al., 2005; Weston, 2012). The multiple etiologies and the interaction of various factors involved in periosteal new bone formation complicate its interpretation in bioarchaeological research; nevertheless, bioarchaeologists

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often assess periosteal lesions when reconstructing health in the past.

Periosteal lesions are often used by bioarchaeologists as non-specific indicators of physiological stress in response to endogenous or exogenous stressors (Larsen, 1997). Viewing these lesions as non-specific indicators of stress and thus not diagnosing the specific cause of periosteal lesions for each individual in a skeletal sample ignores potential variation in morbidity and mortality among those exhibiting the lesions and prevents examination of the relationship between specific diseases and morbidity and mortality (Powell, 1988; Weston, 2012). Nonetheless, the "non-specific" approach can still yield important insights about health and mortality in past populations. For example, previous research has shown that, at least in medieval samples from England and Denmark, periosteal lesions are associated with elevated risks of mortality (DeWitte and Wood, 2008; Usher, 2000). It is important to note that Usher's study pooled data on both destructive and proliferative periosteal new bone formation lesions for analysis, rather than focusing just on proliferative lesions, so her results are not necessarily directly comparable with other studies that do focus strictly on proliferative lesions. Given that under conditions of both normal (i.e. non-epidemic) medieval mortality and during the 14th-century Black Death, individuals with tibial periosteal lesions were more likely to die than their age peers without these lesions (DeWitte and Wood, 2008), it appears that periosteal lesions can be viewed as a marker of poor health or high frailty (frailty is defined as an individual's risk of death relative to other members of the population (Vaupel et al., 1979), and individuals with higher frailty are less likely to survive while those with lower frailty are more likely to survive).

In bioarchaeological studies, periosteal lesions are often scored as woven (unremodeled and thus reflecting active disease or inflammatory responses at the time of death) or sclerotic (lamellar or remodeled and thus indicative of healing by the time of death or a chronic disease process) or a combination of the two (Buikstra and Ubelaker, 1994). For the previous studies of the relationship between periosteal lesions and risk of mortality (DeWitte and Wood, 2008; Usher, 2000), data on active, mixed, and healed lesions were pooled for analysis, an approach that is typical in bioarchaeology and often reflects a need to maximize sample sizes for analysis. Thus, what was missing from these studies is an assessment of whether there are survival differentials between individuals who had active periosteal lesions at their time of death and those who had healed lesions, even though there is reason to suspect such a differential might exist.

Several researchers have suggested that the activity (active vs. healed) of skeletal lesions in general (i.e. not just periosteal lesions) might be informative about underlying differences in health or heterogeneity in frailty. For example, (Mays et al., 2002) view remodeled periosteal new bone formation as indicative of individuals who survived longer with disease compared to those with woven bone lesions. Wood et al. (1992) argue that healed skeletal lesions in general might, at least under some circumstances, reflect relatively good health and low frailty as they reflect the survival of a disease process earlier in life (see also the comment by Eisenberg in response to Wood et al.). Based on the distributions of healed vs. active periosteal lesions by age among children below the age of four from a Late Woodland site, Wood et al. suggest that individuals with healed lesions were less likely to die than those with active lesions. Similarly, Novak and Šlaus (2010) found that among subadults from a Roman-period site in Croatia, active periosteal lesions were more frequent among those between the ages of 0–4.9, whereas healed lesions were more common in the 5–14.9 year age group. (Rose, 1985) observed systemic active periosteal lesions (or "infection") more frequently in subadults compared to adults, and more healed infection in the latter than the former. In medieval Croatian samples, children (between the ages 1 and 11.5 years) with healed periosteal lesions or healed cribra orbitalia had larger dimensions (e.g. diaphyseal lengths adjusted for age) than those with active lesions (Pinhasi et al., 2013). It is possible that both relatively large bone dimensions and healed lesions indicate relatively low underlying frailty. Grauer (1993) reported that healed periosteal lesions and porotic hyperostosis were more common in adults (ages 20–65) in a British medieval sample. Mittler and Van Gerven (1994) discovered in medieval Nubian samples that active cribra orbitalia lesions were limited to infants and children and that older individuals exhibited healing lesions; however, this age pattern might be a reflection of the fact that cribra orbitalia typically only develops during childhood rather than an indication of underlying levels of frailty. Several studies of tooth crown size have reported that juveniles have smaller permanent teeth than adults in the same assemblages (Guagliardo, 1982; Stojanowski et al., 2007). Small crown size can indicate that an individual did not achieve maximum genetic potential because of exposure to developmental stressors, and the smaller size permanent teeth in juveniles suggests higher risks of mortality for those exposed to such stressors (Stojanowski et al., 2007). Relatively large teeth might be considered analogous to absent or healed lesions, given that they can indicate individuals who either avoided developmental stress or survived it and still developed normally despite it. It should be noted that not all previous research has revealed patterns suggestive of survival or health advantages associated with healed skeletal lesions. Shuler (2011), for example, found more healed than active periosteal lesions in adolescents when compared to adults in a 17th–19th-century slave cemetery.

Though several researchers have argued or inferred that healed lesions may indicate lower frailty, to date no study has explicitly and quantitatively tested differences in survival or mortality rates across all ages between those with active versus healed periosteal lesions. Other studies have considered age in the analysis of the *presence* of skeletal stress markers, including but not limited to periosteal lesions (e.g. Cucina et al., 1997; Goodman and Armelagos, 1988; Jankauskas, 2003; Lallo et al., 1978; Novak and Šlaus, 2010; Paine et al., 2007; Pinhasi et al., 2006; Roberts et al., 1998; Steckel et al., 2002; Temple, 2010), but fewer studies have simultaneously examined age patterns and the activity of stress markers. This study builds upon the few previous studies that have examined age patterns of healed and active periosteal lesions by more directly assessing the relationship between periosteal lesion activity and survival. It addresses the question: does the presence of healed or healing periosteal lesions indicate substantial survival advantages in general? Using data from medieval London cemeteries, this study tests the hypothesis that individuals with healed periosteal lesions had higher survivorship compared to those with active lesions.

2. Materials and methods

2.1. Skeletal samples

All skeletal samples ($n = 538$) for this study come from medieval London cemeteries and are curated at the Museum of London Centre for Human Bioarchaeology.

2.1.1. East Smithfield (1349–1350)

The East Smithfield cemetery from east London is one of only a few excavated European cemeteries with both strong documentary and archaeological evidence clearly linking it to the 14th-century Black Death, and it was founded before the arrival of the epidemic for the express purpose of burying victims of the Black Death (Grainger et al., 2008; Hawkins, 1990). Archaeological excavations disinterred over 600 individuals from East Smithfield. Stratigraphic evidence indicates that the East Smithfield burials were completed in a single phase, and there is no evidence of interments after 1350 (Grainger et al., 2008), so it can be safely assumed that most, if not all, of the individuals interred in East Smithfield cemetery died as the result of the Black Death. This study of 187 individuals from East Smithfield includes all the excavated individuals from the cemetery who were sufficiently well preserved to be scored for skeletal indicators of age and the presence of periosteal lesions, using the methods described below. The same criteria also determined the sample sizes from most other cemeteries used in this study; the exception is the St. Mary Spital cemetery, as detailed below.

Given the extraordinarily high mortality levels caused by the Black Death, the East Smithfield sample does not reflect normal mortality patterns and thus represents different mortality conditions than those that produced the other cemeteries used in this study. However, previous research using East Smithfield found similar patterns in both the East Smithfield cemetery and a normal mortality sample with respect to the relationship between periosteal lesions and risks of mortality (DeWitte and Wood, 2008), and thus inclusion of the East Smithfield might have no effect on the results of this study. Nonetheless, given that the East Smithfield sample might include people who were otherwise relatively healthy and thus would not likely have died under normal mortality conditions, it is possible that the relationship between periosteal lesion activity and survival observed in this study might be affected by the presence of Black Death victims. Because of this, analyses were performed both with and without the East Smithfield sample to confirm the consistency of the estimated patterns.

2.1.2. Guildhall Yard (c. 1050–1230)

The Guildhall Yard site is located in central London. It was the site of the lay cemetery for St. Lawrence Jewry (WORD database, 2012). Excavations between 1992 and 1997 yielded a total of 68 individuals, the vast majority of whom were interred in one of two time periods, 1050–1140 or 1140–1230. This study includes 31 individuals from Guildhall Yard.

2.1.3. St. Mary Graces Cemetery (c. 1350–1538)

The Cistercian Abbey of St. Mary Graces was established in London shortly after the first outbreak of the Black Death ended in London in 1350 and was in use until the Reformation in 1538 (Grainger and Hawkins, 1988; Grainger et al., 2008). A cemetery associated with the Abbey of St. Mary Graces was used for burial of members of the general population, and monks and important lay people were buried within the Abbey's church and chapels (Grainger and Hawkins, 1988; Grainger and Phillpotts, 2011; Rogers and Waldron, 2001). Excavation of St. Mary revealed several hundred skeletons from within the Abbey church and chapels and from the larger lay cemetery (Grainger and Hawkins 1988; Grainger and Phillpotts 2011). This study uses a sample of 128 individuals from the St. Mary Graces cemetery.

2.1.4. St. Mary Spital (c. 1120–1540)

The site of St. Mary Spital was located outside the eastern walls of the City, close to Bishopsgate. There are two burial areas associated with the site, the larger of which (referred to here as the St. Mary Spital cemetery) contained over 10,000 burials, including lay individuals, infirmary patients, and members of the priory of St. Mary Spital (i.e. canons, lay staff, residents and benefactors) (Connell et al., 2012). The St. Mary Spital cemetery has been divided into four periods using Bayesian radiocarbon dating: 14 (*c.* 1120–1200), 15 (*c.* 1200–1250), 16 (*c.* 1250–1400) and 17 (*c.* 1400–1539), and there are both single and multiple burials within in each period (Connell et al., 2012). A random sample of 400 individuals (200 from each period) was selected for preliminary analysis for this study. Of those, a pooled sample of 192 single inhumations from periods 15 and 17 were sufficiently preserved to be scored for skeletal indicators of age and the presence of periosteal lesions and were thus included in this study.

2.2. Age estimation

Adult ages (i.e. ages for individuals with fused epiphyses and erupted permanent dentition) were estimated using the method of transition analysis described by Boldsen et al. (2002). Though based on the same skeletal features (such as the pubic symphysis) as traditional methods of adult age estimation, transition analysis was designed to avoid the biases associated with traditional methods, i.e. age mimicry, underestimation of older adult ages, and overestimation of younger adult ages (Boldsen et al., 2002). Further, and of particular importance for studies of survival across the lifespan, transition analysis provides point estimates of age, even for the oldest adult ages, rather than broad interval estimates. In transition analysis, data from a known-age reference collection are used to obtain the conditional probability, $\Pr(c_j|a)$, that a skeleton will exhibit a particular age indicator stage or suite of age indicator stages given the individual's known age. This conditional probability is combined, using Bayes' theorem, with a prior distribution of ages at death to estimate the posterior probability that a skeleton in the cemetery sample died at a certain age given that it displays particular age indicator stages. This prior distribution of ages at death can either be a uniform prior or an informative prior based on documentary data. The application of Bayes' theorem in this way means that age estimation avoids imposing the age distribution of the reference sample on the target sample (age-mimicry), and is thus preferable to traditional methods of age estimation (Boldsen et al., 2002).

For this study, transition analysis was applied to skeletal age indicators on the pubic symphysis and the iliac auricular surface and to cranial suture closure as described by Boldsen et al. (2002). The ADBOU (Anthropological Database, Odense University) Age Estimation software was used to determine individual ages-at-death and the standard errors associated with those point estimates. The ADBOU program uses a conditional probability estimated from the Smithsonian Institution's Terry Collection that an individual at a given age will be in the observed age indicator states. The program also uses an informative prior distribution of ages at death based on data from 17th-century Danish rural parish records.

Age estimates for pre-adults were based on the diaphyseal lengths of major long bones for fetal and neonatal remains between ages 10 and 50 gestational weeks, epiphyseal fusion, and dental development and eruption (Gustafson and Koch, 1974; Moorrees et al., 1969; Scheuer et al., 1980; Scheuer and Black, 2000; Smith, 1991).

2.3. Periosteal new bone formation

As described in the Introduction (Section 1), periosteal new bone formation occurs in response to stimuli that traumatize the periosteum and as a result of local or systemic infection or inflammation associated with a variety of factors. Though it is desirable in some cases to undertake differential diagnosis in order to attribute periosteal lesions to specific diseases, that approach was not used for the current study, as the objective here is to establish whether active or healed periosteal lesions in general are associated with survival. In future research, it might prove productive to examine the relationships between periosteal lesion activity and survival or mortality in the context of specific, diagnosable diseases, but that is beyond the scope of this paper.

For this study, periosteal lesions were scored on the tibia because of the robust nature and thus typical good general preservation of this bone and because previous work has demonstrated the relatively high frequency with which the tibia is affected by such lesions (Eisenberg, 1991; Galloway et al., 1997; Larsen, 1997; Roberts and Manchester, 2005; Stojanowski et al., 2002; Willey et al., 1997). Scoring for periosteal lesions was limited to the anterior surfaces of the tibial diaphysis. The posterior surface and epiphyses were excluded in order to avoid incorrectly scoring minor muscle attachments. Periosteal lesions were identified macroscopically under good lighting and scored as present if the there was at least one distinct patch, of any size, of woven or sclerotic bone laid down on the surface of the diaphysis. The periosteal lesions were scored as woven (active) if the patch of bone appeared porous with sharp, unremodeled edges; lesions were scored as sclerotic (healed) if the patch of bone had rounded, remodeled edges (Weston, 2008). When scoring for periosteal lesions on the diaphyses of pre-adults, particular care was taken to only assess the bone at least one centimeter away from the epiphyseal growth plates to minimize the potential for confusing porosity associated with normal growth for periosteal new bone (Ortner et al., 2001).

Only tibiae with diaphyseal surfaces that were free of both periosteal lesions and postmortem damage were scored as lacking periosteal lesions; tibiae with no visible lesions but with postmortem damage that prevented visual assessment of the entire anterior surface were given a score of "unobservable" with respect to periosteal lesions and thus excluded from analysis. As mentioned above, periosteal lesions can have infectious or traumatic causes. Traumatic injuries are more likely to result in unilateral manifestations of periosteal lesions whereas infectious causes are more likely to cause bilateral lesions (Larsen, 1997; Weston, 2012). In an effort to restrict these analyses to periosteal lesions that are more likely the result of infectious causes and thus lesions that are presumed to be more reflective of underlying immune competence (or lack thereof), only individuals for whom both right and left tibiae were observable were scored for periosteal lesions.

Although scoring periosteal lesions in pre-adults sought to reduce the potential for incorrectly scoring porosity associated with normal growth as periosteal lesions, it is possible that the pre-adult subsample for this study contain false positives for periosteal new bone formation. To control for the possible inclusion of false positives for periosteal lesions among pre-adults, analyses used both a sample that included all ages and a sample that excluded individuals below the age of 15.

2.4. Kaplan–Meier survival analysis

The effect of periosteal lesion activity (no lesions, healed lesions, a mixture of both healed and active lesions, or active lesions) on survival was assessed through Kaplan–Meier survival analysis with a log rank test using pooled data on point estimates of age and periosteal lesion activity from all cemetery samples. Analysis was performed using SPSS version 21. As mentioned in Section 2.3, analyses included both a sample of all individuals and a sample that included those above the age of 15 to verify that any observed differences (or lack thereof) in survival were not an artifact of incorrectly scoring porosity associated with normal growth as active lesions. Lastly, as mentioned in Section 2.1.1, analyses were also repeated using a sample that excluded the individuals from the East Smithfield cemetery to control for the potential effects of catastrophic mortality.

3. Results

3.1. Periosteal new bone formation frequencies

Table 1 provides the age distribution of the frequencies of individuals without periosteal lesions, and those with active, mixed, and healed periosteal lesions. The age intervals shown in Table 1 are used only to reveal general patterns and not for analytical purposes; point-estimates of age, rather than age intervals, were used for Kaplan–Meier survival analysis. In these cemeteries, none of the individuals above the age of 30 had active lesions without signs of healing.

Table 1
Frequencies of individuals with no periosteal lesions and those with active, mixed (i.e. a mixture of active and healed), and healed lesions. The numbers in the parentheses are the percent of individuals in the corresponding age interval within each periosteal lesion category.

Age	Absent (%)	Active (%)	Mixed (%)	Healed (%)	Total
0–9.99	32 (0.561)	7 (0.123)	17 (0.298)	1 (0.018)	57
10–19.99	88 (0.607)	9 (0.062)	32 (0.221)	16 (0.110)	145
20–29.99	59 (0.562)	0 (0)	18 (0.172)	28 (0.267)	105
30–39.99	67 (0.523)	0 (0)	22 (0.139)	39 (0.305)	128
40–49.99	7 (0.292)	0 (0)	3 (0.125)	14 (0.583)	24
50–59.99	3 (0.375)	0 (0)	3 (0.375)	2 (0.250)	8
60–69.99	12 (0.522)	0 (0)	2 (0.087)	9 (0.391)	23
70+	17 (0.354)	0 (0)	12 (0.250)	19 (0.396)	48
Total	285	16	109	128	538

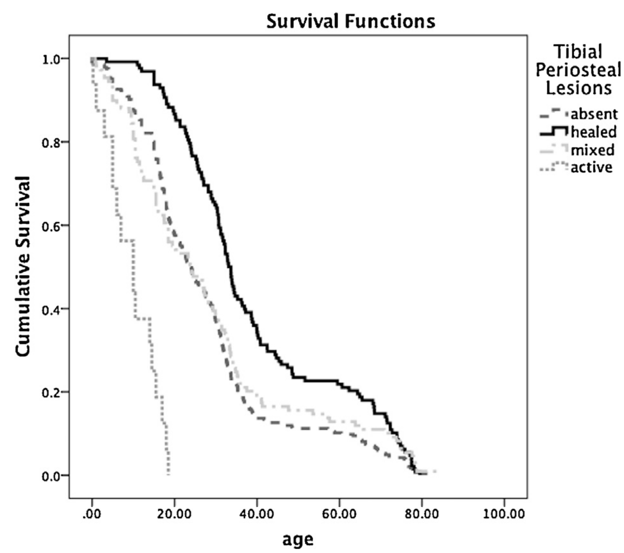

Fig. 1. Kaplan–Meier survival curves for sample including all ages from all cemeteries.

3.2. Kaplan–Meier survivorship

The results of Kaplan–Meier survival analysis are shown in Table 2, and the survival curves for the samples including individuals from all cemeteries (i.e. including East Smithfield) are shown in Figs. 1 and 2. The results from the analyses using samples that include and exclude individuals from the East Smithfield Black Death cemetery are consistent; the corresponding Kaplan–Meier survival analysis results are also provided in Table 2.

The results of analyses including all ages and those including just individuals above the age of 15 both reveal significant differences in mean survival time among the various periosteal presence and activity categories. Based on these results, individuals can be organized from lowest to highest survivorship as follows: active periosteal lesions, absence of lesions, mixed lesions, and healed lesions (i.e. without any signs of active lesions). In all analyses, the mean survival time for those with active lesions at the time of death is substantially lower than that for all other categories, and the corresponding 95% confidence interval for those with active lesions does not overlap at all that of any other category. There is also a clear distinction in the mean survival times between those without any

Table 2
Kaplan–Meier survival analysis results.

Sample	Periosteal lesion activity	Mean survival time	95% CI	Mantel–Cox χ^2	*p*-value
All cemeteries, all ages	Absent	27.7	25.7–29.8	91.3	<0.001
	Active	9.7	6.7–12.7		
	Mixed	28.4	24.4–32.5		
	Healed	39.3	35.9–42.7		
All cemeteries, ≥15	Absent	32.5	30.3–34.8	34.1	<0.001
	Active	17.3	16.0–18.5		
	Mixed	37.0	32.4–41.5		
	Healed	40.3	36.9–43.7		
Excluding East Smithfield, all ages	Absent	27.3	24.1–30.4	70.8	<0.001
	Active	9.5	5.6–13.4		
	Mixed	33.4	28.7–38.1		
	Healed	39.8	36.1–43.5		
Excluding East Smithfield, ≥15	Absent	33.9	30.5–37.4	24.5	<0.001
	Active	17.3	15.5–19.2		
	Mixed	38.6	33.8–43.4		
	Healed	40.4	36.7–44.1		

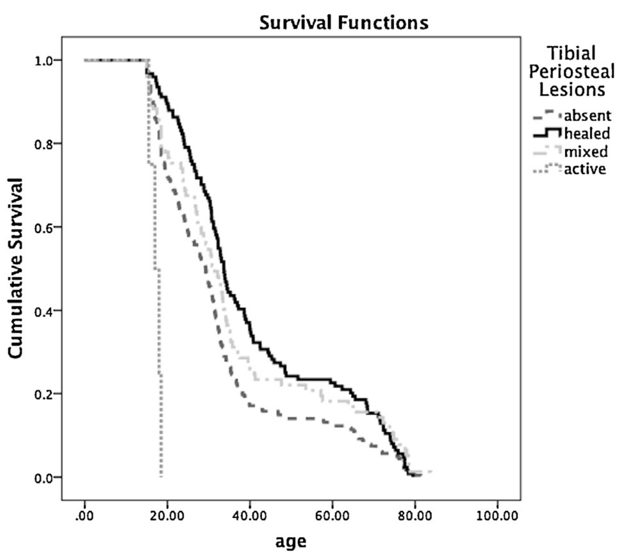

Fig. 2. Kaplan–Meier survival curves for sample including just the adults from all cemeteries.

periosteal lesions and those with healed lesions for most samples. The one exception is the sample of adults that excludes individuals from East Smithfield, in which case there is an overlap of the 95% confidence intervals for individuals without lesions, those with mixed lesions, and those with only healed lesions. For the sample including all ages and all cemeteries, the 95% confidence interval for the mean survival time of those with mixed lesions overlaps that of the individuals without periosteal lesions but not with that of individuals with only healed lesions. However, for the remaining three analyses, the 95% confidence interval for the mean survival time of individuals with mixed lesions overlaps that of both the individuals with healed lesions and those without any lesions.

4. Discussion

The results of this study indicate that there are substantial differences in survivorship between people with healed periosteal lesions and those with active lesions. There are also survival differences between those with healed lesions and those without any lesions. In the medieval population of London, it appears that individuals with healed periosteal lesions had higher survivorship compared to both those with active lesions and those without any lesions at all. These results are consistent across most of the analyses using samples that include all ages, those that exclude individuals below the age of 15, and those both with and without victims of the 14th-century Black Death. The results from the sample of adults that excludes Black Death victims does not reveal a clear distinction in survivorship among those without lesions, those with mixed lesions, and those with healed lesions, though perhaps this is an artifact of the relatively small sample size ($n = 288$) of adult individuals buried in cemeteries other than East Smithfield.

It is perhaps surprising that the results indicate the highest survivorship among individuals with healed lesions, rather than those with no lesions as all, as it might make intuitive sense that individuals without periosteal lesions would have the lowest frailty and thus the highest survivorship. Indeed, such an interpretation of these and other skeletal lesions is frequently made in many bioarchaeological investigations. However, the highest estimated survivorship among individuals with healed periosteal lesions might reflect a generally low underlying level of frailty among individuals in this group. That is, as suggested by Wood et al. (1992) and Ortner (1991), individuals with healed periosteal lesions might have had the greatest ability to survive certain physiological stressors long enough such that skeletal lesions, which formed in response to those stressors, had an opportunity to heal. The higher survival of individuals with healed lesions compared to those without any lesions suggests that the absence of lesions might, in some cases, indicate relatively high frailty, i.e. some individuals in this population without lesions were too frail to survive the associated physiological stressors long enough for a lesion to form in response. These results do not necessarily mean that the absence of periosteal lesions should always be interpreted as indicating relatively high frailty. Rather, the results might indicate that the group of individuals without periosteal lesions includes sufficient numbers of people with high frailty (and thus low survivorship) to produce a discernable difference in survival between those with healed lesions and those without any lesions.

A few previous bioarchaeological studies have revealed positive associations between periosteal lesions and adult age (though no distinction was made in those studies between active and healed lesions). For example, Rose and Hartnady (1991) found that tibial periosteal lesions increased in frequency with adult age in a historic Afro-American cemetery from Arkansas; the authors interpreted this pattern as a reflection of diminishing disease resistance with increasing adult age in the population. In a medieval sample from northern England, Grauer (1993) similarly reported that the frequency of periosteal lesions increased with older adult age, and she argues that this indicates the accumulation of nonlethal conditions that are sufficient to cause periosteal lesions with age.

Grauer also suggests that the positive association between age and periosteal lesions might reflect a selection process whereby individuals capable of withstanding certain physiological stressors survive to adulthood with skeletal evidence of those past stressors. Recent analysis of skeletal samples from medieval London also revealed a significant positive relationship between age and periosteal lesions (DeWitte, 2014). These observed age patterns of periosteal lesions are consistent with the estimates obtained here of enhanced survival among those with healed periosteal lesions compared to those without.

The results of this study reveal a continuum of survivorship from an absence of lesions to mixed lesions to healed lesions, as the 95% confidence intervals for the estimated survival for those without periosteal lesions overlaps that of individuals with mixed lesions in all analyses. Most analyses revealed no substantial difference in survival between those with healed lesions and those with a mixture of both healed and active lesions. Such a continuum across these three categories might reflect heterogeneity in frailty within each and makes it difficult to make any conclusions about survival differentials between those with mixed lesions versus those without lesions or with healed lesions. However, there is a common pattern of clear distinctions in survival among those with active, completely absent, and completely healed lesions.

The fact that several of these analyses revealed no substantial difference in survival between those with healed lesions and those with a mixture of both healed and active lesions suggests that the presence of healing is an indicator of relatively low frailty. To put it another way, the results of this study indicate that it is the presence of *active* lesions without any evidence of healing that is the best marker of relatively high frailty. Perhaps this distinction between the presence or absence of *healing* is what paleopathological and bioarchaeological studies should emphasize, rather than merely the presence or absence of periosteal lesions. The lowest estimated survivorship among those with active lesions might reflect a variety of causes of high frailty, such as underlying susceptibility to infection associated with nutritional deficiencies, intrinsic (i.e. genetically or developmentally determined) poor immune competence, previous exposure to disease, or some other detrimental environmental factor.

It is possible that the observed difference in survival between those with active periosteal lesions (with no signs of healing) and those with only healed lesions exists because each of these categories is associated with different etiologies in these particular samples. As mentioned in Section 2.3, differential diagnoses were not performed for this study, and thus I have not controlled for different causes of periosteal lesions here. Weston (2008) found that lesion type (woven, lamellar, or mixed) was not associated with any particular underlying disease (e.g. rickets, syphilis, chronic osteomyelitis, osteoplastic periostitis), but rather reflected the healing process irrespective of etiology. Nonetheless, it is possible that in this study, the active lesions reflect acute, more highly deadly disease episodes whereas the healed lesions are caused by less severe diseases or other non-fatal physiological stressors. Perhaps bioarchaeologists interested in particular diseases might determine survival differentials associated with active versus healed lesions in the contexts of those diseases. For other bioarchaeologists, who by choice or by necessity (because of the limitations of sample size or degree of preservation) continue to use periosteal lesions as a marker of non-specific physiological stress, attention should be paid to the age distribution of active and healed lesions when interpreting results.

The results of this study suggest a relationship between periosteal lesions and survival that is more complex than the relationship that is typically described, or at the very least implicitly assumed, in many bioarchaeological investigations. For example, a recent analysis of the association between periosteal lesions and periodontal disease (DeWitte and Bekvalac, 2011) revealed a positive association between the two pathologies that was independent of the effects of age. The association between the two pathologies was interpreted as perhaps reflecting underlying immune competence and thus susceptibility to pathogens that caused either periodontal disease or infections that result in periosteal lesions (i.e. individuals with both pathologies had poor immune competence and thus relatively high susceptibility to infection), exposure to an deleterious environmental factor (e.g. unsanitary living conditions), or underlying heightened inflammatory responses that made some individuals both more likely to develop new periosteal bone in response to trauma or infection and periodontal disease when challenged with periodontal pathogens. However, in that study, as in most other bioarchaeological studies that incorporate analysis of skeletal lesions, no distinction was made during the analysis phase between active and healed lesions. It is possible that it was only active periosteal lesions that were truly positively associated with periodontal disease, and that the inclusion of individuals with healed periosteal lesions in the analysis simply did not mask the observed relationship between the pathologies. Resolving whether this was actually the case would necessitate further analyses. Regardless, the results of this study should not be viewed necessarily as contradicting the findings of previous investigations that have found an association between periosteal lesions and poor health or elevated risks of mortality. Rather, this study should stimulate additional research in a variety of temporal and geographic contexts wherein a distinction between active and healed lesions is maintained.

The results of analyses that excluded Black Death victims from East Smithfield are similar to the results obtained using the larger sample. This indicates that inclusion of epidemic victims did not strongly affect the patterns observed in this study, which is consistent with previous research indicating that mortality during the Black Death behaved similarly to normal medieval mortality in targeting frail individuals (DeWitte and Hughes-Morey, 2012; DeWitte and Wood, 2008).

5. Conclusion

The results of this study reveal distinct survival differences between individuals with active and healed periosteal lesions. These findings indicate that it would be productive to examine not just presence of periosteal lesions but also their activity in analyses of frailty, and heterogeneity thereof, in past populations, and particularly to view active lesions with no signs of healing as markers of relatively high frailty.

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