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Background: Heterotopic ossification in the extremities remains a common complication in the setting of high-energy wartime trauma, particularly in blast-injured amputees and in those in whom the definitive amputation was performed within the zone of injury. The purposes of this cohort study were to report the experience of one major military medical center with high-energy wartime extremity wounds, to define the prevalence of heterotopic ossification in these patients, and to explore the relationship between heterotopic ossification and other potential independent predictors.

Methods: We retrospectively reviewed the records and radiographs of all combat-wounded patients admitted to this institution between March 1, 2003, and December 31, 2006. Patients with a minimum of two months of radiographic follow-up who underwent at least one orthopaedic procedure on an extremity constituted our study group; those who underwent at least one orthopaedic procedure but had not had heterotopic ossification develop constituted the control group. Variables recorded for each study subject included age and sex, location and mechanism of injury, method(s) of fracture fixation, number of débridement procedures, duration of negative pressure therapy, location of heterotopic ossification, presence and severity of traumatic brain injury, and Injury Severity Scores.

Results: During the study period, 1213 war-wounded patients were admitted. Of those patients, 243 (157 in the heterotopic ossification group and eighty-six controls) met the inclusion criteria. The observed rate of heterotopic ossification was 64.6%. A significant relationship was detected between heterotopic ossification and the presence ($p = 0.006$) and severity ($p = 0.003$) of a traumatic brain injury. Risk factors for the development of heterotopic ossification were found to be an age of less than thirty years ($p = 0.007$, odds ratio = 3.0), an amputation ($p = 0.048$, odds ratio = 2.9), multiple extremity injuries ($p = 0.002$, odds ratio = 3.9), and an Injury Severity Score of ≥16 ($p = 0.02$, odds ratio = 2.2).

Conclusions: The prevalence of heterotopic ossification in war-wounded patients is higher than that in civilian trauma. Although trends associated with local wound conditions were identified, the risk factors for the development of heterotopic ossification found in this study suggest that systemic causes predominate.

Level of Evidence: Prognostic Level II. See Instructions to Authors for a complete description of levels of evidence.

Heterotopic ossification in the extremities is a common complication in the setting of high-energy wartime extremity trauma[1], and substantial amounts of time and resources are directed toward prophylaxis and treatment[2-6]. Recent literature has suggested that the prevalence may be higher than previously reported, particularly inblast-injured amputees and in those in whom the definitive amputation was performed within the zone of injury[6]. While the rate of het-

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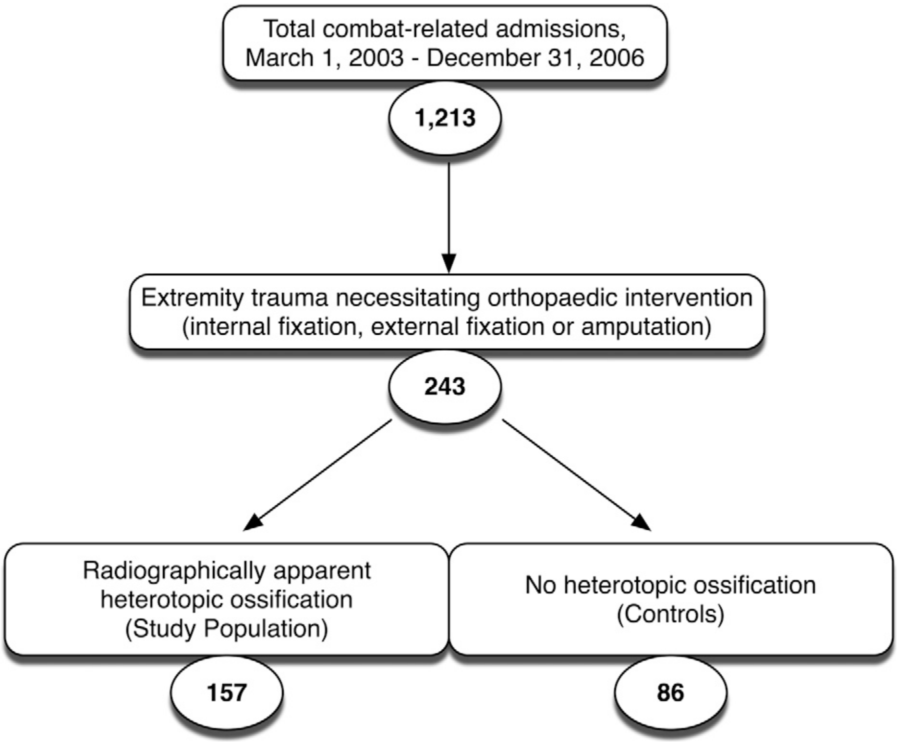

Fig. 1

Flowchart illustrating the selection of study participants and controls.

erotopic ossification in combat-related amputations has been established, epidemiologic data on the bulk of war-wounded patients have not yet been published as far as we know.

Heterotopic ossification has been associated with concomitant head injuries, deep muscle dissection in the setting of arthroplasty or open reduction and internal fixation of femoral fractures, familial disorders, and neoplasm[7-16]. The relationship between severe head injury and heterotopic ossification has been studied extensively; however, data related to less severe traumatic brain injury are lacking[17-22]. As traumatic brain injuries are common following wartime blast exposures[23-25], the relationship between the quantifiable traumatic brain injury score and the development of heterotopic ossification deserves closer study[24-28].

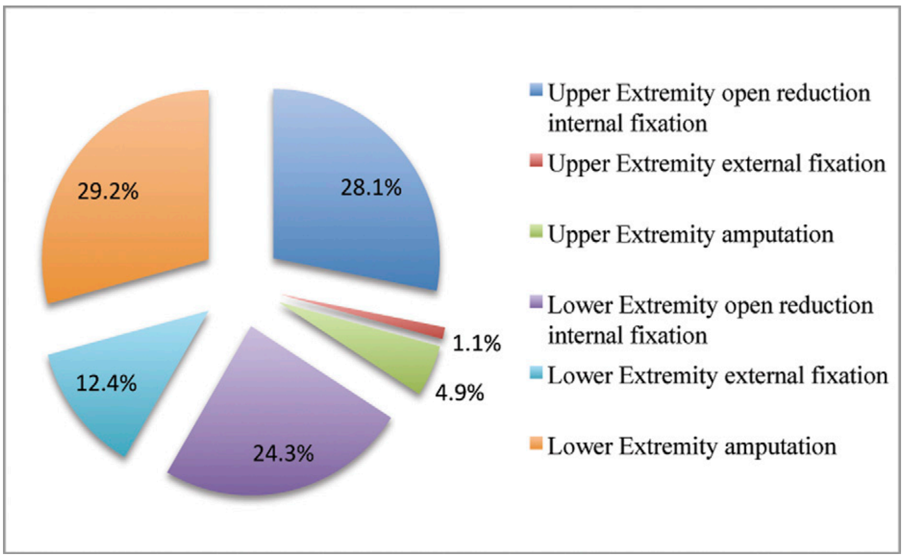

Fig. 2

Distribution of heterotopic ossification in the study group by operative site and the method of definitive treatment.

TABLE I Univariate Analysis of Dependent Variables and the Development of Heterotopic Ossification

Characteristic	No. of Patients (N = 243)	Patients with Heterotopic Ossification (N = 157)	Control Subjects without Heterotopic Ossification (N = 86)	P Value
Age* *(yr)*		23.7 ± 4.7	25.6 ± 7.2	0.01†
Injury Severity Score*		18.0 ± 12.3	12.0 ± 8.7	<0.001†
No. of débridement procedures*		5.2 ± 3.10	3.72 ± 2.84	<0.001†
Duration of negative-pressure wound therapy* *(days)*		10.9 ± 10.4	6.51 ± 8.14	<0.001†
Injury Severity Score category				<0.001‡
Score of <16	140	79 (56%)	61 (44%)	
Score of ≥16	97	75 (77%)	22 (23%)	
Sex				0.67‡
Male	241	156 (64.7%)	85 (35.3%)	
Female	2	1	1	
Multiple affected limbs				<0.001‡
No	194	115 (59%)	79 (41%)	
Yes	49	42 (86%)	7 (14%)	
Mechanism of injury				0.06§
Blast	186	127 (68%)	59 (32%)	
Crash	13	8	5	
Crush	6	4	2	
Fall	9	2	7	
Gunshot wound	29	16 (55%)	13 (45%)	
Traumatic brain injury				0.006‡
No	155	98 (63%)	57 (37%)	
Yes	66	50 (76%)	16 (24%)	
Traumatic brain injury category				0.003§
Mild	34	30 (88%)	4 (12%)	
Moderate	19	14	5	
Severe	13	6	7	
Multiple fracture fixation methods				0.15‡
No	207	130 (62.8%)	77 (37.2%)	
Yes	36	27 (75%)	9 (25%)	
Blast and Injury Severity Score of ≥16				0.02‡
No	96	60 (63%)	36 (38%)	
Yes	83	65 (78%)	18 (22%)	
Traumatic brain injury and Injury Severity Score of ≥16				0.02‡
No	122	84 (69%)	38 (31%)	
Yes	24	22 (92%)	2 (8%)	
Blast and traumatic brain injury				0.04‡
No	90	62 (69%)	28 (31%)	
Yes	36	31 (86%)	5 (14%)	

*The values are given as the mean and the standard deviation. †Student t test. ‡Chi-square test. §Fisher exact test.

Another area of concern regarding heterotopic ossification and high-energy long-bone fractures is the method of definitive fracture fixation. Because heterotopic ossification is thought to result from muscle injury that can occur during the surgical approach[7,14,29-37], it is possible that in multiply injured patients, internal fixation carries an increased risk compared with definitive external fixation, especially when internal fixation is delayed[38]. Although heterotopic ossification is a known complication of both external fixation and internal fixation[39-41], we are not aware of any data comparing the two in high-energy

TABLE II Univariate Analysis of 315 Wounds in 243 Patients*

Location and Type of Orthopaedic Procedure	No. of Wounds	Group with Heterotopic Ossification (N = 185)	Control Group without Heterotopic Ossification (N = 130)
Upper extremity open reduction and internal fixation	92	52 (57%)	40 (44%)
Lower extremity open reduction and internal fixation	73	45 (62%)	28 (38%)
Upper extremity external fixation	3	2	1
Lower extremity external fixation	35	23 (66%)	12 (34%)
Upper extremity amputation	30	9 (30%)	21 (70%)
Lower extremity amputation	82	54 (66%)	28 (34%)

*Associations between categorical variables were studied on a per-wound basis with use of the Fisher exact test. Lower extremity groups were significantly different, compared with corresponding upper extremity groups, with regard to location and type of orthopaedic procedure ($p = 0.023$).

extremity trauma. Also, it is not known whether other independent predictors including those validated in civilian trauma, such as the Injury Severity Score[42,43], apply to patients sustaining high-energy wartime extremity trauma[2,3,6]. Finally, the hypothesis that wound débridement techniques, including pulsatile lavage and negative-pressure wound therapy, contribute to the development of heterotopic ossification has not been examined objectively[6,44].

The purposes of this retrospective cohort study were to report the experience of one major military medical center with high-energy wartime extremity wounds, to define the prevalence of heterotopic ossification in the extremities of these patients, and to explore the relationship between heterotopic ossification and potential risk factors, such as mechanism(s) of injury, the number of débridement procedures, the duration of continuous negative-pressure wound therapy, definitive surgical treatment rendered, the Injury Severity Score, and the traumatic brain injury score.

Materials and Methods

Study Methodology

The institutional review board at the National Naval Medical Center approved this study. We retrospectively reviewed the medical records; the International Classification of Diseases, Ninth Revision (ICD-9) codes; Common Procedural Terminology (CPT) codes; and radiographs of all combat-wounded patients admitted to the National Naval Medical Center in Bethesda, Maryland, between March 1, 2003, and December 31, 2006. Patients who underwent at least one orthopaedic procedure on an extremity constituted our study group. For the purpose of this study, an orthopaedic procedure was defined as one of the following surgical interventions: open reduction and internal fixation, definitive external fixation, or amputation. Those who underwent at least one orthopaedic procedure on an extremity but did not have heterotopic ossification develop constituted the control group. Patients with

TABLE III Multivariate Nominal Logistic Regression Analysis of Factors Predicting Heterotopic Ossification in 243 Patients*

Characteristic	P Value	Chi Square	Odds Ratio
Patient age (continuous variable)	0.01†	6.4	N/A
Age of <30 yr compared with ≥30 yr (odds ratio for <30 years)	0.007†	7.4	3.0
Injury Severity Score (continuous variable)	<0.001†	13.9	N/A
Injury Severity Score of <16 compared with ≥16 (odds ratio for an Injury Severity Score of ≥16)	0.02†	5.4	2.2
Multiple affected limbs (odds ratio for multiple affected)	0.002†	10.1	3.9
Location (odds ratio for residual limb)	0.048†	6.1	2.9
Mechanism of injury	0.25		
Blast and Injury Severity Score of ≥16	0.26		
Traumatic brain injury and Injury Severity Score of ≥16	0.69		
Blast and traumatic brain injury	0.37		

*Only the factors identified to be potentially significant ($p < 0.05$) on categorical contingency analysis were entered into the multivariate model in order to determine whether they were independent predictors for the development of heterotopic ossification. †The difference was significant ($p < 0.05$).

insufficient medical record documentation or radiographic follow-up of less than two months were excluded. The severity of heterotopic ossification was graded by adapting the method proposed by Potter et al., as it is most easily applied to the residual limbs of amputees[6]. Involvement was graded as mild (<25% of the width of the residual soft tissues), moderate (25% to 50% of the width of the residual soft tissues), or severe (>50% of the width of the residual soft tissues) with use of a single (anteroposterior, lateral, or oblique) radiograph. The best available radiograph that maximized the two-dimensional radiographic shadow of ectopic bone was used for grading.

Variables recorded for each study subject included age, sex, location and mechanism of injury (a blast mechanism, such as an improvised explosive device, rocket-propelled grenade, or land mine, or a nonblast mechanism, such as a gunshot wound, motor-vehicle crash, crush injury, or fall), duration of continuous negative-pressure wound therapy, number of débridement procedures, method(s) of fracture fixation, location of heterotopic ossification, presence and severity of traumatic brain injury, and Injury Severity Score (mild, moderate, or severe). Traumatic brain injury assessment was performed independently according to the Department of Defense traumatic brain injury criteria[28].

Statistical Analysis

Associations between categorical variables were studied with the Student t test, Fisher exact test, or chi-square test, as appropriate. The clinical outcome studied was the presence of heterotopic ossification. To assess the independent predictive effect of a covariate for a nominal response (development of heterotopic ossification), a logistic regression model was constructed and parameters estimated with use of maximum likelihood. Only the factors identified to be potentially significant ($p < 0.05$) on categorical contingency analysis were entered into the multivariate model in order to determine the independent prognostic effect of these variables for the development of heterotopic ossification. Odds ratios were calculated for the maximum likelihood parameter estimates. A p value of <0.05 was considered significant.

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Results

During the study period, 1213 war-wounded patients were admitted to this institution. Of those patients, 243 (157 patients in the heterotopic ossification group and eighty-six controls) met the inclusion criteria (Fig. 1). The average duration of follow-up for the heterotopic ossification group (mean, 8.4 months; range, two to forty-one months) was similar to that of the control group (mean, 7.1 months; range, two to thirty-six months) ($p = 0.25$). The wounds predominantly involved the lower extremity (60.3% of the patients) compared with the upper extremity (39.7%), and 20.2% of the patients sustained trauma in multiple limbs. The observed rate of heterotopic ossification development was 64.6% (157) of 243 patients and 12.9% (157) of 1213 patients overall. The distribution of heterotopic ossification by operative site and procedure is depicted in Figure 2.

Demographic Data and Risk Factors

The analyses of dependent variables are summarized in Tables I and II. Multivariate analyses are summarized in Table III. The average age of the study participants was 24.4 years (range, eighteen to fifty-three years). Thirty-five patients (14.4%) in our cohort were over thirty years old. Age was shown to be a significant variable (mean and standard deviation, 23.7 ± 4.7 years for the heterotopic ossification group compared with 25.6 ± 7.2 years for the control group; $p = 0.01$). In fact, a patient age of less than thirty years was independently predictive of heterotopic ossification development on multivariate analysis ($p = 0.007$, odds ratio = 3.0).

Location, Injury Severity, Traumatic Brain Injury Score, and Blast Injury in the Study Group Compared with the Controls

The location of injury was determined to be a significant predictor of heterotopic bone formation. Those with lower extremity trauma ($p < 0.023$) and those with an amputated limb ($p = 0.048$, odds ratio = 2.9) were at increased risk for the development of heterotopic ossification. Additionally, multiple extremity injuries correlated with the development of heterotopic ossification on both univariate ($p < 0.001$) and multivariate analyses ($p = 0.002$, odds ratio = 3.9). Thirty-six patients (14.8%) underwent multiple orthopaedic fracture fixation procedures (e.g., open reduction and internal fixation revisions, or hardware removal and conversion to definitive external fixation), but there was no apparent relationship between the number of surgical procedures and heterotopic ossification formation ($p = 0.15$). There was also no apparent relationship between the method of definitive fracture fixation (internal or external) and the development of heterotopic ossification ($p = 0.77$).

Injury severity was significantly worse in the heterotopic ossification group. The mean Injury Severity Score for those with heterotopic ossification was 18.0 ± 12.3 compared with 12.0 ± 8.7 for the control group ($p < 0.001$). Multivariate analysis (Table III) revealed that an Injury Severity Score of ≥16 was predictive of heterotopic ossification development ($p = 0.02$, odds ratio = 2.2).

Traumatic brain injury scores were available for 221 of the 243 patients meeting the inclusion criteria. The relationship between the development of heterotopic ossification and both the presence ($p = 0.006$) and the severity ($p = 0.003$) of a traumatic brain injury was significant on univariate but not multivariate analysis.

The relationship between a blast injury and heterotopic ossification development approached significance ($p = 0.06$); however, a blast mechanism of injury with a concomitant Injury Severity Score of ≥16 ($p = 0.02$) or traumatic brain injury ($p = 0.04$) was predictive of heterotopic ossification on univariate analysis.

Number of Débridement Procedures and Duration of Negative-Pressure Wound Therapy

Patients who had heterotopic ossification develop underwent more débridement procedures (mean [and standard deviation], 5.20 ± 3.10) compared with the control group (mean, 3.72 ± 2.84) ($p < 0.001$). Similarly, the heterotopic ossification group underwent a longer duration of negative-pressure wound therapy (mean, 10.9 ± 10.4 days) compared with controls (mean, 6.51 ± 8.14 days) ($p < 0.001$).

Discussion

The prevalence of heterotopic ossification in this patient group (64.6%) remains far greater than that reported in civilian extremity injuries. The results of this study are similar to the military amputee data reported by Potter et al., further confirming that the prevalence of heterotopic ossification (63% of 213 amputees) is higher in wartime injuries compared with those sustained in civilian settings[6]. In perhaps the largest civilian series examining fracture care and heterotopic ossification, Garland reported that heterotopic ossification occurred in the extremities in 11% of patients with a severe traumatic brain injury and 20% of patients with spinal cord injury[45]. His earlier work described rates of ectopic bone development in various long-bone fractures, including forearm fractures (20%)[46], femoral shaft fractures (52%)[47], and tibial shaft fractures (0%)[48], all of which were observed in patients with concomitant head injury.

Few case series evaluating both patients with a fracture and a head injury and those with a fracture and without a head injury have contained a control group for comparison. Spencer compared the healing times and radiographic callus appearance in eighty-two fractures in fifty-three patients with a head injury and those of extremity fractures in thirty patients with no head injury[49]. On the basis of the graphical representation of his data, an exuberant healing response was present in 52.6% of tibial fractures, 60% of femoral fractures, and 36.4% of humeral fractures in patients with a head injury compared with an average of 10% across the three fracture sites in patients without a head injury. He also demonstrated a decreased time to union in the head-injured group and concluded that the term heterotopic ossification may be more appropriate in describing exuberant fracture callus. Giannoudis et al. reproduced these findings in patients with a femoral fracture, noting a shorter time to union and a higher callus-to-diaphyseal ratio in patients with a head injury compared with controls without a head injury[50]. We are aware of no consensus regarding the rate of heterotopic ossification in long-bone extremity trauma without a head injury. Nevertheless, the prevalence in this setting is generally considered to be low[17,49-51].

Although this study demonstrated a significant increase in the rate of development of heterotopic ossification in patients with an age of less than thirty years ($p < 0.007$, odds ratio = 3.0), the bulk of the available literature does not support any association with age[6,52-59], and the literature supporting an age association suggests an increased risk for the development of heterotopic ossification with advancing age[60-62]. Simonsen et al. reported opposite results, noting an increased risk in younger adult patients[43]. The age-related results in the present study may have been subject to a selection bias as our patient group is skewed toward young men.

The predilection of heterotopic bone formation in the residual limbs of amputees ($p = 0.048$, odds ratio = 2.9) is an important observation. It is our opinion that, although wounds may be equally matched between upper and lower extremities, the latter are often subject to more severe injury patterns. Both upper and lower extremity amputations, however, are often performed within or near the zone of injury (which is extensive in blast injuries) in an effort to preserve length. Potter et al., in their retrospective study of 373 combat-related amputations, reported an association between the performance of the definitive amputation within the zone of injury and the subsequent development of symptomatic heterotopic ossification[6].

Regarding traumatic brain injury, investigators have noted an increased osteogenic potential and enhanced fracture-healing in head-injured patients, although the precise mechanism remains unknown[63-65]. Hendricks et al. correlated the presence of heterotopic ossification to the severity of closed head injuries[66], but, in general, data linking the development of heterotopic ossification to milder forms of traumatic brain injury are lacking. The results of our study suggest that, although the presence of traumatic brain injury alone may be associated with the development of heterotopic bone, it is not an independent predictor. This study was also unable to establish a difference between patients with mild traumatic brain injuries and those with no traumatic brain injury. More research is needed, specifically to clarify this association.

The Injury Severity Score was identified as an independent predictor of the development of heterotopic ossification. Despite a historic association[67], critics of the Injury Severity Score as a predictor for heterotopic ossification have maintained that head-injured patients score higher and, therefore, are inherently more likely to have heterotopic bone develop. Using regression analysis, Steinberg and Hubbard reported that the Injury Severity Score, independent of a head injury, was a predictor of the development of heterotopic ossification of the hip after intramedullary femoral nailing[51]. Likewise, the multivariate analysis performed in this study identified that an Injury Severity Score of ≥16 ($p = 0.02$, odds ratio = 2.2) and the presence of multiple extremity injuries ($p = 0.002$, odds ratio = 3.9) were both predictive of heterotopic ossification development.

This cohort of patients demonstrated a trend associated with an increase in both the number of débridement procedures ($p < 0.001$) as well as the duration of negative-pressure wound therapy ($p < 0.001$). In this series, patients with more severe systemic injury patterns (i.e., with an Injury Severity Score of ≥16) underwent a similar number of débridement procedures and required a similar duration of continuous negative-pressure wound therapy compared with those in the study group who ultimately had heterotopic ossification develop. We believe that the greater number of débridement procedures and longer duration of negative-pressure wound therapy observed in this study are more likely an indicator of the severity of the local injury than a mechanism for the development of ectopic bone.

The literature has focused on heterotopic ossification following pelvic and hip trauma as well as select surgical approaches[7,14,29-32,34-37]; however, it seems reasonable that, although a substantial portion of wartime soft-tissue trauma occurs at the time of injury, additional soft-tissue trauma in the form of multiple surgical débridements as well as muscle dissection during internal fixation may result in a higher degree of muscle damage and may lead to an increased prevalence of heterotopic ossification. The converse then should also hold true, that external fixation or amputation may result in less heterotopic bone formation. This study was unable to discern a relationship between the type of definitive fracture treatment and the formation of heterotopic ossification in this particular patient group.

This study is limited by its retrospective design. It is also likely that sampling bias exists for two reasons. First, patients referred to our institution tend to be more severely wounded than those who proceed directly to smaller military treatment facilities for definitive care. Second, our institution receives the majority of patients with penetrating and severe head trauma within the military health-care system. We acknowledge that this sampling bias may artificially elevate the reported prevalence of heterotopic ossification, and thus it may not apply to the service members who sustain less severe injuries treated at smaller hospitals. Additionally, prior to 2005, traumatic brain injury scores were recorded only at the request of the treating surgeons and were not routinely recorded on all trauma admissions until midway through the study period. As a result, milder traumatic brain injuries, less obvious to the treating surgeon, may be underrepresented in this cohort. Furthermore, limitations inherent to the Department of Defense traumatic brain injury criteria may overestimate the numbers of moderate and severe traumatic brain injuries. As a result, the association between the severity of traumatic brain injury and heterotopic ossification reported in this study with use of these criteria should be interpreted with caution. Also, in order to provide comprehensive, timely, multidisciplinary care for these patients, a large number of general and orthopaedic surgeons participated in the treatment of these wounds; thus, treatment regimens were not standardized. Finally, on discharge from this institution, patients recover and receive follow-up care at numerous military, civilian, and Veterans Administration hospitals across the country. Therefore, determining an accurate rate of symptomatic heterotopic ossification is extremely difficult in a military cohort.

In conclusion, the prevalence of heterotopic ossification in war-wounded patients is higher than in civilian trauma. Although trends associated with local wound conditions were identified, risk factors for the development of heterotopic ossification found in this study suggest that systemic causes predominate. ■

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