# Investigating the incidence and magnitude of heterotopic ossification with and without joints involvement in patients with a limb fracture and mild traumatic brain injury

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## ARTICLE INFO

## ABSTRACT

*Objectives:* This study seeks to evaluate the incidence rate of heterotopic ossification (HO) formation in patients afflicted by an isolated limb fracture (ILF) and a concomitant mild traumatic brain injury (mTBI).
*Methods:* The current study is an observational study including ILF patients with or without a concomitant mTBI recruited from an orthopedic clinic of a Level 1 Trauma Hospital. Patients were diagnosed with a mTBI according to the American Congress of Rehabilitation Medicine (ACRM) criteria. Radiographs taken on average 3 months post-trauma were analyzed separately by two distinct specialists for the presence of HO proximally to the fracture site (joints or extra joints). Both raters referred to Brooker's and Della's Valle's classification to establish signs of HO. First, analyses were conducted for the full sample. Secondly, a matched cohort was used in order to control for specific factors, namely age, sex, type of injury, and time elapsed between the accident and the analyzed radiograph.
*Results:* The full sample included a total of 183 patients with an ILF (94 females; 47.5 years old), of which 50 had a concomitant mTBI and 133 without. Radiographic evidence of HO was significantly higher in patients with an ILF and a mTBI compared to ILF patients ($X^2 = 6.50$; $p = 0.01$). The matched cohort consisted of 94 participants (i.e.; 47 patients from the ILF + mTBI group and 47 patients from the ILF group). Again, ILF + mTBI patients presented significantly higher rates of HO signs in comparison to ILF patients ($X^2 = 3.69$; $p = 0.04$). Presence of HO was associated with prolonged delays to return to work (RTW) only in ILF + mTBI patients (F = 4.055; $p = 0.05$) but not in ILF patients (F = 0.823; $p = 0.37$).
*Conclusions:* Study findings suggest that rates of HO are significantly higher proximally to fracture sites when ILF patients sustain a concomitant mTBI, even after controlling for factors known to influence HO. Moreover, results show that HO is associated with a prolonged RTW only in ILF patients with a concomitant mTBI but not in ILF-only patients. The impact of mTBI on HO formation warrants further attention to detect early signs of HO, to identify shared physiopathological mechanisms and, ultimately, to design targeted therapies.

## 1. Introduction

Heterotopic ossification (HO), defined as an abnormal bone formation occurring in extra-skeletal tissues, is a possible complication following fractures (Kaplan et al., 2004). The risk of developing HO varies depending on the type of fracture, with incidence of HO reaching nearly 40% in patients with elbow fractures (Eisenstein et al., 2018; Foruria et al., 2013, 2014). HO develops around the fracture site, more typically near a joint, making certain fractures, such as elbow and hip fractures, more prone to HO formation (Pape et al., 2004). As a result, most studies have investigated HO in this context and the impact of fractures occurring away from joints on HO remains less known.

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Clinical manifestations of HO, including soft-tissue loss, joint contractures, motion deficits, stiffness, and chronic pain, can become a debilitating condition for the affected patients (Vanden Bossche and Vanderstraeten, 2005). HO has been associated with reduced quality of life mainly due to extended medical treatment and higher probability of undergoing additional surgical procedures to remove heterotopic bone (Winkler et al., 2015). It is therefore not surprising that HO has been identified as a major obstacle to rehabilitation (Nauth et al., 2012).

HO initially follows similar physiological patterns as the natural fracture healing process (Nauth et al., 2012). However, HO's pathological mechanisms are thought to originate from the convergence of multiple factors including prolonged nervous system and immune system responses to injury (Forsberg et al., 2014; Convente et al., 2015; Kraft et al., 2016; Sullivan et al., 2013). More precisely, recent studies suggest that HO results from exaggerated inflammatory cytokine release, osteoprogenitor cell proliferation due to inflammation, increased leptin levels, vascularization of injured tissues, and the activation of bone morphogenic protein (BMP) signaling, all known to promote bone formation in extra-skeletal locations (Eisenstein et al., 2018; Nauth et al., 2012; Firoozabadi et al., 2017).

Traumatic brain injury (TBI) is a known risk factor for the development of HO in polytrauma patients (Dizdar et al., 2013; Coelho and Beraldo, 2009; Ranganathan et al., 2015; Bajwa et al., 2018). Recent estimates suggest that nearly 20% of patients who suffer from TBI or spinal cord injuries will develop HO (Cipriano et al., 2009). Moreover, concomitant limb fracture and TBI is associated with a twofold increase risk of HO occurrence (Foruria et al., 2014; Dizdar et al., 2013). A possible explanation for the high occurrence of HO in orthopedic patients with a TBI is the overlapping physiopathological mechanisms involved in both injuries, namely dysfunctions in the blood-brain barrier permeability, substance P increase, and prolonged pro-inflammatory cytokine release, making the physiological environment more prone to HO formation (Huang et al., 2018; Evans et al., 2012). These pathological mechanisms are also observed after the mildest form of TBI, the mild TBI (mTBI).

MTBIs account for approximately 70–90% of all TBIs sustained and are frequent among patients who suffered from fractures, with an incidence rate estimated at 23% (Cassidy et al., 2004; Jodoin et al., 2016). Although considered the mildest form of TBIs, a growing body of evidence shows that concomitant mTBI can have a significant impact on recovery in patients with fractures, highlighting the importance of considering the interaction between these two injuries (Jodoin et al., 2017a,b). To our knowledge, the association between mTBI and HO has not been investigated. Lack of medical follow-ups after mTBIs, subclinical HO signs associated with less severe accidents as well as underdiagnosed mTBI in trauma patients presenting with fractures could partly underlie this lack of scientific interest (Jodoin et al., 2016). Here, we tested whether isolated limb fracture patients (ILF) presenting with a concomitant mTBI have a higher incidence rate of HO when compared to ILF patients without a mTBI.

## 2. Methods

### 2.1. Participants selection

All participants included in this study were selected from a previous sample recruited consecutively from a single orthopedic clinic of a Level 1 Trauma Hospital to evaluate the incidence rate of mTBI among ILF patients (For more details; Jodoin et al., 2016). Each participant has consented to grant access to their research data for future studies. This sample consisted of 251 participants with an ILF of which 58 participants had suffered from a mTBI based on the American Congress of Rehabilitation Medicine (ACRM) clinical criteria (loss of consciousness, loss of memory for the events immediately before or after the accident, and alteration of mental state at the time of the accident) (Carroll et al., 2004). A mTBI diagnosis was given when a patient reported at least

three of the four abovementioned criteria. Moreover, patients' medical files were also screened to gather more information related to the accident and to the injuries. Patients were eligible to take part in this study if they had suffered from an ILF and did not meet any of the exclusion criteria, namely being under 18 years old, substance-related intoxication at the emergency room, Glasgow Coma Scale under 13 at emergency admission, health-related complications other than mTBI in the acute and post-acute injury phases, and non-extremity fractures (hip, pelvis, ribs, neck, spinal cord, and skull). Moreover, patients were excluded from the analyses if they presented with signs of HO prior to the accident and if raters were unable to distinguish between bone fragment and HO. The study was approved by a local ethics committee.

### 2.2. Characterization of HO

Participants were included from the initial sample only if radiographs were taken at least 45 days post-trauma. This cut-off was set as signs of HO can be adequately detected at that time (Cipriano et al., 2009). Moreover, in cases of multiple radiograph availabilities for a single patient, the radiograph conducted the closest to three months post-trauma was selected considering that medical check-ups are frequent at this time and that it falls within the range when HO formation is typically best detected (Cipriano et al., 2009). Radiographs of all patients were analyzed separately by a trained senior orthopaedist resident and a senior orthopedic surgeon both blind to the subjects' group classification. To evaluate signs of HO, both raters used a specialised radiology display system (NEC Display Solutions; MultiSync Monitor LCD 2090UXi-20.1; Made in China) to detect the presence of abnormal bone formation located in extra-skeletal soft tissues. More specifically, signs of HO were sought for near the fracture location, independently of joints involvement (see Fig. 1 for a representative case of HO among the current sample). Hypertrophic callus was excluded from HO cases as the ossification identified needed to be at the heterotopic site and not at the fracture callus itself. In addition, Brooker's and Della Valle's classifications were used conjointly as suggested by Toom et al. (2005) aiming to improve inter-observer reliability in the assessment of HO. Inter-rater reliability was verified and reached an almost perfect agreement according to Cohen's kappa coefficient (k = 0.93). In case of disagreements among raters, both raters reviewed together the radiograph to reach an agreement concerning the presence of HO formation.

### 2.3. Matched sample procedure

Further steps were taken to control for potential factors known to affect the risk of HO formation. Patients from the ILF + mTBI group were matched with ILF patients according to age, sex, type of injury (area of fracture), and time elapsed between the accident and the radiograph. The importance of matching for the delay between the accident and the analyzed radiograph is to control for the risk of HO signs developing after the analyzed radiograph (Cipriano et al., 2009). To do so, we proceeded by using a one-on-one matching approach based on the following criteria: 1) age ( ± 5 years); 2) sex; 3) type of injury (area of fracture); 4) time elapsed between the accident and the radiograph ( ± 14 days). A match was made when all four criteria corresponded for two participants from each experimental group (ILF + mTBI group and ILF group). When more than one participant from the control group matched with a ILF + mTBI patient based on the aforementioned criteria, we selected the control participant who corresponded most closely to the ILF + mTBI patient. This matching process allowed to form 47 near-identical pairs. The remaining participants who were not matched according to the criteria were excluded from these analyses.

### 2.4. Analyses

Descriptive analyses were used to characterize and compare the two

**Fig. 1.** Representative case of HO among sample.

**Table 1**
Descriptive characteristics of full study cohort by group.

| | Total | mTBI | No TBI | *P*-value |
|---|---|---|---|---|
| N (subjects) | 183 | 50 | 133 | – |
| Age (years [SD]) | 47.5 (15.5) | 43.8 (15.3) | 48.9 (15.3) | 0.75 |
| Sex (Female [%]) | 94 (51.4) | 19 (38.0) | 75 (56.4) | 0.02* |
| Surgical procedures (% of sample) | 32.7 | 26.8 | 34.6 | 0.23 |
| Delay between trauma and analyzed radiograph (days) | 86.8 | 87.2 | 86.7 | 0.92 |

* = Level of significance was set at p < 0.05

groups from our study (ILF + mTBI group and ILF group). Results from descriptive analyses are expressed as means, SD (standard deviation), and percentages (refer to Tables 1–2). We used Pearson chi-square tests to compare the incidence rate of HO between the two experimental groups (ILF + mTBI group and ILF group). Additional chi-square analyses were conducted to evaluate the possible impact of sex, age group (18–24; 25–44; 45–64; 65+ years old), joint involvement (periarticular fracture versus diaphyseal fracture) and surgical procedures on HO formation. A linear regression analysis was computed to give an estimate on which independent variable, mTBI or joint involvement, best predicted HO development. Statistical tests were carried out with a α-level fixed at 0.05. The same pattern of analyses was used to test the study hypothesis among the matched sample. Moreover, a 2 × 2 ANOVA was used to assess the impact of HO and mTBI on return to work (RTW) among the matched sample. RTW was used in this study to reflect potential impact of HO development on functional outcome as it is known to be a good marker of recovery (Clay et al., 2010).

**Table 2**
Distribution of fracture characteristics.

| Body distribution of fractures [Number of patients] | Total | mTBI | No TBI |
|---|---|---|---|
| - Metacarpal | 2 | 1 | 1 |
| - Metatarsal | 11 | 3 | 8 |
| - Proximal humerus | 21 | 7 | 14 |
| - Humerus diaphysis | 5 | 1 | 4 |
| - Distal humerus | 6 | 0 | 6 |
| - Scapula | 3 | 2 | 1 |
| - Clavicle | 18 | 11 | 7 |
| - Proximal ulna | 5 | 2 | 3 |
| - Ulna diaphyseal | 3 | 2 | 1 |
| - Distal radius | 45 | 8 | 37 |
| - Femur | 2 | 1 | 1 |
| - Patella | 2 | 1 | 1 |
| - Proximal tibia | 4 | 2 | 2 |
| - Diaphyseal tibia | 7 | 3 | 4 |
| - Distal tibia | 9 | 2 | 7 |
| - Ankle | 40 | 4 | 36 |

| Joint involvement | Total | mTBI | No TBI | P-value |
|---|---|---|---|---|
| - Yes (periarticular fracture) | 146 | 30 | 116 | 0.01 |
| - No (diaphyseal fracture) | 37 | 20 | 17 | |

Information on RTW was collected in the context of a previous study conducted by our group (see Jodoin et al. (2017b) for more details). Statistical analyses were performed using IBM SPSS software version 24 (Armonk, NY, United States).

## 3. Results

### 3.1. Results of full sample analysis

A total of 183 participants were selected, from a study cohort of 251 individuals recruited by our group (see participant flowchart in Fig. 2). The remaining participants were excluded from the current study due to the inability to access their radiograph. Among the final sample, 50 patients were in the ILF + mTBI group (females = 19; mean age = 43.8) and 133 patients were in the ILF group (females = 75; mean age = 48.9). On average, radiographs were analyzed 86.8 days post-trauma (range: 45 days–201 days), a delay that was similar between groups (F = 0.01; p = 0.92) (see Table 1). There was a significantly higher rate of periarticular fractures, as opposed to diaphyseal fractures, in the ILF group compared to the ILF + mTBI group ($X^2$ = 16.69; p = 0.01) (see Table 2). This difference can be mainly attributed to the low rate of ILF + mTBI patients with ankle and distal radius fractures, compared to the ILF patients. Given the higher incidence of mTBI in fractures occurring proximally to the head (Jodoin et al., 2016), risks of suffering from a mTBI are rare in individuals treated for ankle and distal radius fractures.

Patients in the ILF + mTBI group showed significantly more signs of HO compared to patients with an ILF alone (X = 6.50; p = 0.01), with the majority of patients presenting with low grade HO according to Brooker's and Della's Valle's classification (see Tables 3–4). The incidence rates of HO signs were 46.0% in ILF + mTBI patients (23/50) as opposed to 26.3% in patients with an ILF alone (35/133). Of note, sex ($X^2$ = 2.32; p = 0.10), age group ($X^2$ = 2.08; p = 0.56), and surgical procedures ($X^2$ = 1.71; p = 0.13) were unrelated to the detection of signs of HO. Furthermore, rates of HO signs were found to be similar whether the fracture occurred proximally (periarticular fracture) or distally (diaphyseal fracture) to a joint ($X^2$ = 1.68; p = 0.24). See Table 5 for more details. Lastly, results from the computed linear regression analysis show that sustaining a concomitant mTBI significantly predicted risks of HO development (β-coefficient = 0.18; t = 2.29; p = 0.02), whereas joint involvement was unrelated to HO development (β-coefficient = −0.05; t = −0.56; p = 0.58).
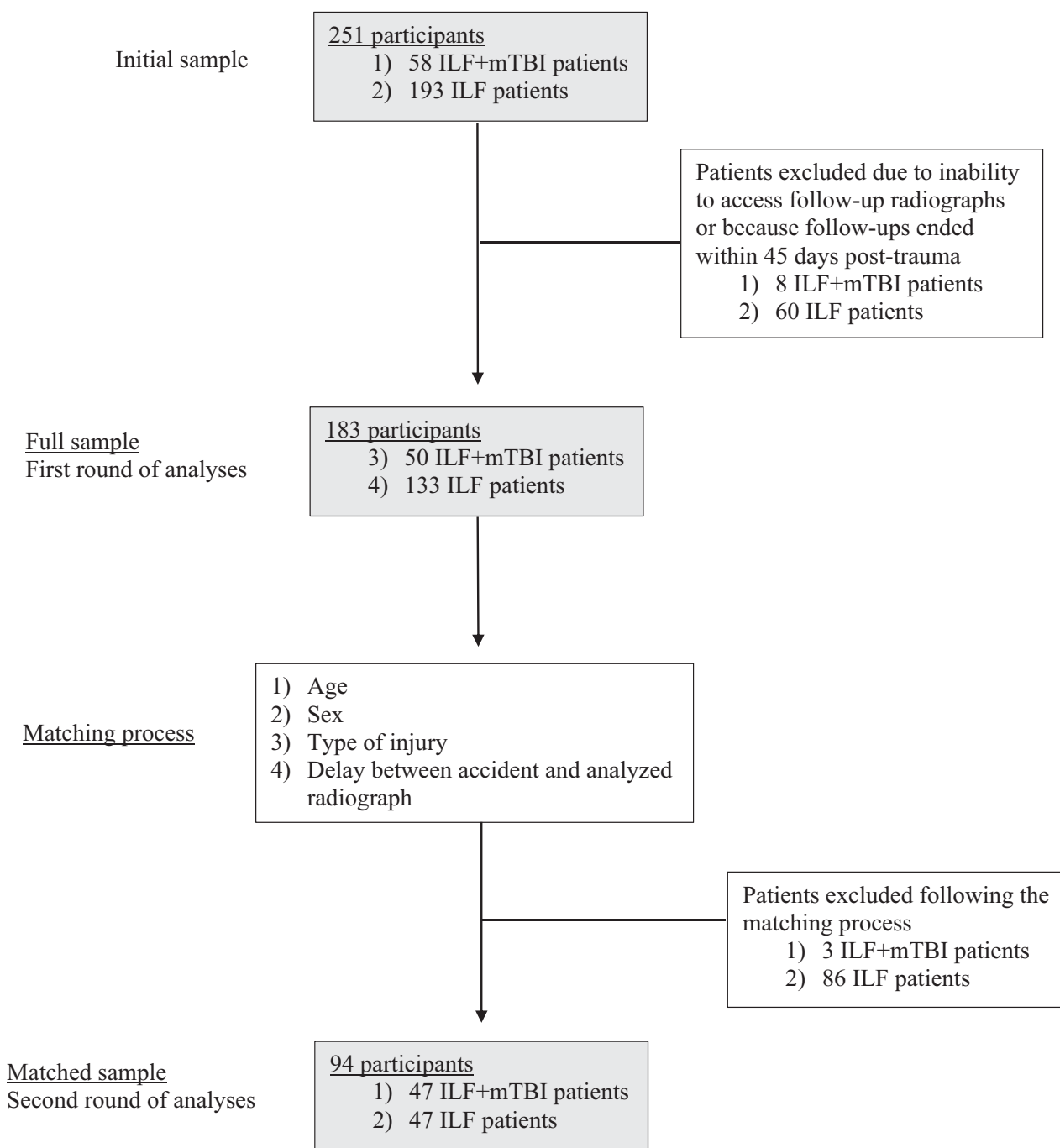
**Fig. 2.** Participant selection flowchart.

**Table 3**
HO signs among full sample.

|  | mTBI | No TBI | $X^2$ | P-Value |
|---|---|---|---|---|
| HO signs (Number of patients [%]) | 23/50 (46.0) | 35/133 (26.3) | 6.50 | 0.01* |

\* = Level of significance was set at p < 0.05

### 3.2. Results of analyses from the matched sample

A total of 94 participants were matched (i.e.; 47 patients from the ILF + mTBI group and 47 patients from the ILF group). Participants from both groups were equivalent according to the following criteria:

age ($t = 0.00$; $p = 1.00$), sex ($X^2 = 0.00$; $p = 1.00$), area of injury ($X^2 = 0.00$; $p = 1.00$), and delay between the accident and the analyzed radiograph ($t = 1.08$; $p = 0.30$). Groups did not differ based on rates of surgical procedures ($X^2 = 1.73$; $p = 0.25$). Refer to Table 6 to obtain detailed descriptive characteristics regarding the matched sample.

Similar to results obtained with the full sample, HO incidence was significantly higher in ILF + mTBI patients in comparison to ILF patients ($X^2 = 3.69$; $p = 0.04$) (see Table 7). This result further supports the notion that concomitant mTBI puts ILF patients at greater risk of developing HO. More specifically, 46.8% of ILF + mTBI patients (22/47) from the matched sample presented signs of HO compared to only 27.7% in ILF patients without a mTBI (13/47). Presence of HO negatively impacted RTW delays in patients with ILF + mTBI (F = 4.055;

**Table 4**
Identification of HO according to Brooker's and Della Valle's classifications.

|  | Total | mTBI | No TBI |
|---|---|---|---|
| Number of subjects per classification |  |  |  |
| - A0 | 124 | 24 | 100 |
| Absence of ossification |  |  |  |
| - A1 | 46 | 20 | 26 |
| Isolated ossifications less than 1 cm in length |  |  |  |
| - B1 | 2 | 2 | 0 |
| Isolated ossifications at least 1 cm in length – leaving MORE than 1 cm distance between pelvis and femur |  |  |  |
| - B2 | 3 | 0 | 3 |
| Marginal ossifications – leaving MORE than 1 cm distance between pelvis and femur |  |  |  |
| - C1 | 3 | 2 | 1 |
| Isolated ossifications at least 1 cm in length – leaving LESS than 1 cm distance between pelvis and femur or ankylosis |  |  |  |
| - C2 | 4 | 2 | 2 |
| Marginal ossifications – leaving LESS than 1 cm distance between pelvis and femur or ankylosis |  |  |  |
| - C3 | 1 | 0 | 1 |
| Ankylosis – leaving LESS than 1 cm distance between pelvis and femur or ankylosis |  |  |  |

**Table 6**
Descriptive characteristics of matched sample by group.

|  | Total | mTBI | No TBI | P-value |
|---|---|---|---|---|
| N (subjects) | 94 | 47 | 47 | – |
| Age (years [SD]) | 43.5 (15.1) | 43.5 (15.5) | 43.5 (14.7) | 1.00 |
| Sex (Female [%]) | 34 (36.2) | 17 (36.2) | 17 (36.2) | 1.00 |
| Surgical procedures (% of sample) | 33.7 | 26.3 | 40.0 | 0.25 |
| Delay between trauma and analyzed radiograph (days) | 92.4 | 98.8 | 86.1 | 0.30 |

**Table 7**
HO signs among matched sample.

|  | mTBI | No TBI | $X^2$ | P-Value |
|---|---|---|---|---|
| HO signs (Number of patients [%]) | 22/47 (46.8) | 13/47 (27.7) | 3.69 | 0.04* |

* = Level of significance was set at $p < 0.05$

$p = 0.05$). Return to work delays did not statistically differ according to the presence of HO in ILF patients without a comorbid mTBI ($F = 0.823$; $p = 0.37$). More specifically, ILF + mTBI patients with HO took, on average, 379 days to RTW compared to 106 days for ILF patients with HO but without a mTBI. As for ILF + mTBI patients without HO, it took, on average, 214 days to RTW as opposed to 168 days for ILF patients without HO and mTBI.

## 4. Discussion

This study investigated the incidence rate of HO among ILF patients with or without a concomitant mTBI. Results from the present study suggest that presence of HO is significantly higher in patients with both trauma injuries (mTBI and ILF) compared to ILF patients, even after controlling for factors known to influence HO, such as age, sex, area of injury, and time elapsed between the accident and the analyzed radiograph. Moreover, results from linear regressions show that sustaining a concomitant mTBI significantly predicts risks for HO development whereas suffering from a fracture near a joint was unrelated. These findings are of particular interest, considering the high prevalence of both injuries, namely ILF and mTBI, and the possible deleterious consequences of HO on recovery and quality of life. In addition, the clinical symptoms linked to HO combined with possible additional surgical procedures to remove the heterotopic bone represent staggering financial burdens (health care expenditures and loss of productivity) (Eisenstein et al., 2018).

Another striking finding from this study is that the combination of HO formation and mTBI was associated with significantly longer RTW delays after an isolated limb fracture. Of note, mTBI without HO also negatively impacted RTW in ILF patients, but to a lesser extent than in the presence of HO. Indeed, results show a near 45% increase in delays to RTW when HO signs were detected in ILF + mTBI patients compared

to ILF + mTBI patients without HO. This is particularly alarming considering that almost half of the assessed patients with an ILF and a comorbid mTBI presented signs of HO. This finding points to the clinical relevance of systematically implementing a follow-up visit at least with ILF + mTBI patients if we are to investigate the impact of mTBI on clinical outcomes associated with HO such as pain, stiffness, and articular amplitude.

Most studies interested in the impact of concomitant TBI on the risk for HO formation focused on polytrauma patients or severely injured patients who suffered from a moderate to severe TBI and mostly focused on HO occurring near a joint (Bajwa et al., 2018; Garland, 1991a,b; Boes et al., 2006). The present study, however, shows that patients with an injury considered less severe, such as an ILF, are significantly more vulnerable to HO formation, regardless of joint involvement, when also afflicted by a comorbid mTBI. To the best of our knowledge, this is the first study specifically investigating the impact of mTBI on HO formation among an orthopedic population. The fact that mTBI typically receives limited medical attention beyond the acute post-accident phase can serve as a possible explanation. Another possibility could be that mTBI patients is not a clinical condition that justifies exposing uninjured bones to X-ray radiation, thus preventing the detection of HO formation in mTBI-alone patients.

From a clinical standpoint, these results shed light on the importance of accounting for the presence of mTBI when treating ILF patients considering that over 44% of patients presenting with both injuries will develop HO. HO presence is classically studied in a context of hip and elbow secondary ankylosis and severe neurological concomitant injury. Although conjectural, this study provides preliminary evidence of the significant impact of mild HO on patient outcome and extends HO screening beyond joints. Importantly, the addition of diaphyseal HO screening provides new information on whole-bone incidence rates of HO following a single fracture. Multiple factors may be at stake with regard to the higher incidence of HO among ILF + mTBI patients. For example, HO is believed to originate from the convergence of multiple mechanisms that closely involve the interaction of the

**Table 5**
Risks of HO in relation to joint involvement.

|  | Periarticular fracture | Diaphyseal fracture | P-value |
|---|---|---|---|
| mTBI |  |  |  |
| - Number of subjects with HO [%] | 14/30 (46.7) | 9/20 (45.0) | 0.57 |
| No mTBI |  |  |  |
| - Number of subjects with HO [%] | 29/116 (25.0) | 6/17 (35.3) | 0.38 |
| P-value | 0.02* | 0.40 |  |

* = Level of significance was set at $p < 0.05$

immune system and the central nervous system (Forsberg et al., 2014; Convente et al., 2015; Kraft et al., 2016; Sullivan et al., 2013). More specifically, a growing body of evidence highlights the involvement of the blood-brain-barrier (BBB) in HO formation (Huang et al., 2018). Interestingly, BBB permeability dysfunction is a well-known consequence of TBI and has been identified as a cause for high incidence rates of HO in patients with moderate to severe TBIs (Toffoli et al., 2008). Recent studies have shown that mTBI also leads to BBB dysfunction which can act as a facilitator in the central nervous system invasion of peripheral immune response substances, such as inflammatory cytokines, following a peripheral insult (Rowe et al., 2016). Additionally, neuroendocrine regulation, a system that is often deficient following mTBI, is closely involved in bone remodeling and HO formation (Undurti et al., 2018). Although speculative, it may be possible that the physiopathology of bone fracture and that of mTBI synergistically interact to promote HO formation. Shedding light on the possible involvement of physiopathological underpinnings of mTBI in HO could help identify new treatment targets and clinical management strategies aiming to minimize HO formation. In this study, HO was most frequently classified as low grade with small bone formation. This level of HO most likely does not cause decreased function by itself. We hypothesize that this low-grade HO is a sign of increased local soft tissue injury and increased neurological inflammation that is secondarily affecting outcome.

One limitation to the current study is that it uses data from participants recruited in the context of a previous study, which potentially restricts study findings generalization. Secondly, collection of prospective data should systematically control for the time elapsed since the injury at the time of radiographs (for example, all taken at three months post-accident) so as to reduce risks for missed HO diagnoses. One interesting avenue in further investigating the relation between RTW delays and HO formation would be to specify the type of work conducted (light versus heavy work) as well as the quality of the RTW (successful RTW versus work accommodations needed). Moreover, investigating RTW delays in relation with both prospective functional recovery measures and low-grade HO could help us identify therapeutic targets for optimal orthopedic trauma recovery. Given that some fractures are more prone to HO formation, larger-scale replication studies should consider data stratification analyses according to injury types. Gained knowledge would allow us to further refine classification of at-risk patients. Finally, future studies should account for additional factors, such as injury severity, duration of immobilization, and pre-injury conditions, such as, but not limited to, history of HO and genetic predisposition, as they are known to impact HO formation (Pape et al., 2004; Dizdar et al., 2013).

## 5. Conclusion

In conclusion, study findings highlight that sustaining a comorbid mTBI puts ILF patients at significantly higher risk of developing HO. Moreover, ILF patients with a mTBI are greatly impacted by HO in relation with RTW, a factor associated with high productivity costs and risks for chronic fracture injury symptoms. This is of significant clinical interest considering the high incidence of both injuries, the frequency at which mTBI goes undiagnosed, and the clinical impact of HO on recovery. The impact of mTBI on HO formation warrants further attention to detect early signs of HO, to identify shared physiopathological mechanisms and, ultimately, to design targeted therapies.

## Conflict of competing interest

None of the authors report any conflict of interest in relation to this paper. The institution of one or more of the authors (HSCM) has received funding from: Arthrex, Conmed, Depuy, Smith and Nephew, Synthes, Tormier, Zimmer.

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## Transparency document

The Transparency document associated with this article can be found, in online version.

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