

Epidemiology of long bone non-unions in Spain[☆]

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ABSTRACT

Epidemiological and ecological studies on long bone non-unions (NU) are scarce, based on different populations and methodologies. The aim of this study was to produce a descriptive analysis of the femur, tibia, and humerus non-union epidemiology in Spain.

Methods Data were obtained from the Minimum Basic Data (Conjunto Mínimo Básico de Datos, CMBD) Hospital Discharge Database of the Spanish Ministry of Health, according to the ICD9-CM coding for diagnoses and procedures, and from the National Institute of Statistics for population, generating secondary databases with the reported cases that included the code 733.82 in a disaggregated manner, by age (categorized in 5 intervals), gender, Spanish region, and calendar year (1997–2015). Percentage of non-unions related to fractures in the previous year, annual prevalence (expressed per 100,000 person-years) and period prevalence (expressed per 100,000 person-period) were calculated by age, gender, and Spanish regions. The Odds ratio (OR) was estimated with a confidence of 95% using a logistic regression model per anatomical site.

Results A mean of 235,446 fractures in all locations were annually reported in Spain from 1997 to 2015. Regarding non-union of long bones (femur, tibia and humerus), a total of 37,053 cases were found, representing a yearly mean of 1,950 cases. The proportion of long bone fractures that evolved into a non-union was 4% (1.4% femur, 1.5% tibia, and 1% humerus). The mean annual prevalence rate of NU in Spain was estimated in 4.5 (3.7–4.9) cases per 100,000 persons-year. The overall NU prevalence in Spain was estimated in 86 cases per 100,000 persons. By the type of bone, the period prevalence (per 100,000 persons-period) of the femur NU was 31, of the tibia 33, and of the humerus 22.

Conclusions This description of the epidemiology of long bone non-unions in Spain confirms that the overall non-union rate has been stable from 2000 to 2015, higher in the tibia and in the femur compared to the humerus. NU occurred more frequently in aged females than in males in the femur and the humerus, while the tibia non-unions were more frequent in males and younger age.

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Introduction

Estimates of non-union (NU) rates between 5 and 10% of the fractures are frequently considered, but scarce data are available about epidemiological and ecological studies on long bone non-unions. A population-based study in Scotland reported an overall non-union incidence rate of 1.9%, but up to 9% in some fractures and some age groups, [1] while a rate of 6.8% readmissions due to non-unions was found in a hospital cohort study in Australia,

[2] and a rate of 4.9% was published from Medicare administrative databases in USA. [3] Variability is evident and accounts for non-union definition, population at risk, and study methodology.

Long bone non-unions are defined as the absence of bone bridging and the presence of a fracture line after nine months from acute fracture, with absence of progressive signs of bone healing over three consecutive months. Before this non-union definition from the Federal Drug Agency (FDA) to assess bone growth stimulator devices, [4] fractures with more than six months without consolidation were frequently considered as non-unions, and the criteria to include non-unions in clinical trials were highly variable.

The importance of non-unions in Public Health derived from the associated morbidity, the prevalence of specific limitations in 40% to 70% of the affected population, [5] and the use and consumption of health resources. [6,7] To understand the cause of non-unions and prevent them, the available cohort and database

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studies have focus in the identification of risk factors, [1,2,8–10] but these may vary depending on the bone, the fracture, or the population characteristics.

The incidence and prevalence of non-unions also vary among studies. Affected bone may associate different non-union rates. Mills et al. [1] found an incidence of 1.3% for pelvis and femur fractures per year, 3% for humerus, and approximately 5.5% for tibia and fibula fractures per year, in a study on data from NHS Scotland Information Services Division. Zura et al. [11] conducted a prospective cohort study on Medicare patients in North Carolina, USA, and the highest rates of non-union were reported in the scaphoid bone (15.5%), the tibia (14%), and the femur (13.9%). Ekegren et al. [2] designed a large study using the Victorian Orthopaedic Trauma Outcomes Registry of Australia to determine the rate of failure of long bone fractures and, according to the type of bone fracture, 2.3% of failures were found in the proximal humerus, 7.8% in the humerus shaft, 4.2% in the subtrochanteric fracture, 13.5% in the femur shaft, 8.4% in the distal femur, and 11.7% in the tibia shaft. Therefore, specific studies may be required to define these rates for a certain population, in a certain health system.

Interestingly, the age at risk may also vary. Higher risk of non-union was found in population from 25 to 44 year, and lower risk in elderly population. [1] But also, from multivariable analysis (adjusted by gender), age group of patients among 55 to 64 year showed 2.44-fold more non-healing risk than the other age groups. [2]

In this context, the aim of this study was to investigate the non-union rates in a secondary national database, and to produce a descriptive analysis of the femur, tibia, and humerus non-union epidemiology in Spain.

Methodology

This is an ecological study, which source of data was the Minimum Basic Data (Conjunto Mínimo Básico de Datos, CMBD) Hospital Discharge Database of the Spanish Ministry of Health, according to the ICD9-CM coding for diagnoses and procedures, and the National Institute of Statistics for population (persons with usual residence in Spain at January the 1st). The secondary databases were obtained in a disaggregated manner by age (categorized in 5 intervals: <15y, 15–44y, 45–64y, 65–74y, >75y), gender (male, female), the Spanish region (17 autonomous regional administrations and 2 autonomous cities – Ceuta and Melilla-), and the calendar year (1997–2015). All the reported cases that included the code 733.82 as one of the twenty diagnoses were requested and obtained. We recovered a total of 80,865 cases with the 733.82 code, of which 2,234 were discarded because a non-union after a fracture was not confirmed, and 41,578 cases because fractures were related to other bones than the femur, tibia, and humerus. Non-union fractures were treated as individual cases.

Counting methodology was used to summarize the total number of non-unions per affected bone, and the total number of fractures of the lower limb and the upper limb. The percentage of non-unions as proportion of the lower limb or upper limb fractures were calculated using a lag of one year, assuming that the acute fracture took place one year before the non-union reporting.

Prevalence of non-unions is considered as a proportion of the Spanish population that required specialized attention in the Spanish Health Services for a femur, tibia, or humerus non-union at any time from 1997 to 2015, or in the overall period (period prevalence). Prevalence ratio compares each regional prevalence with the overall Spanish prevalence, and the odds ratio expresses the likelihood that the non-union will occur in the Spanish population, adjusted by age group and gender.

Annual prevalence (expressed per 100,000 person-years) was calculated using as denominator the total Spanish population per year. Period prevalence (expressed per 100,000 person-period) was calculated by the age, gender, age and gender, and Spanish regions, using as denominator the mean of the population (from 1997 to 2015) for each category of analysis. The prevalence ratio was calculated dividing each regional period prevalence by the overall Spanish prevalence of each fracture type, hence if the prevalence is the same, the ratio is equal to 1; if the prevalence is higher, the ratio is greater than 1; and if the prevalence is lower, the ratio is less than 1.

The Odds Ratio (OR) was estimated with a confidence of 95% using a logistic regression model per anatomical site, considering the non-union fracture (1=present, 0=absent) as the dependent variable, and the age and gender as independent variables. An OR>1 expresses higher risk of non-union (positive association) while an OR<1 expresses a protective factor for non-union (negative association).

Data were described and analysed using the statistical software STATA (StataCorp. 2009. *Stata Statistical Software: Release 11*. College Station, TX: StataCorp LP).

Results

A mean of 235,446 fractures in all the locations were annually reported in Spain during the study period. Regarding non-union of long bones (femur, tibia and humerus), a total of 37,053 cases were reported from 1997 to 2015, representing a mean of 1,950 cases yearly. The proportion of long bone fractures that evolved into a non-union was 4% (1.4% femur, 1.5% tibia, and 1% humerus), after 12 months from the acute fracture report. Fig. 1 shows the total number of long bone non-union fractures registered annually by affected bone, and the percentage of bone healing failure.

The mean annual prevalence rate of NU in Spain was estimated in 4.5 cases per 100,000 persons-year, with a minimum of 3.7 and maximum of 4.9. The mean prevalence rate of femoral NU is 1.6 cases per 100,000 persons-year (min-max:1.2–1.8), that of tibia NU is 1.7 per 100,000 persons-year (min-max:1.6–1.9), and that of humeral NU is 1.2 per 100,000 persons-year (min-max:0.9–1.3). See the tendency by anatomical site in Fig. 2.

The overall NU of long bones distributed by gender showed a proportion of 52% in males and 48% in females. Splitting by affected bone, data showed that 54% of the femur, 33% of the tibia and 60% of the humerus NU occur in females. The prevalence of femur NU and humerus NU are 75% and 49% higher in females than males, respectively. In case of tibia NU, the prevalence in males doubles that in females.

Distributed by age, 64% of the overall NU (n=23,758) occurred in the population from 15 to 64 years. The prevalence rate (per 100,000 persons-period) was 15, 71, 96, 147 and 191 for the <15y, 15–44y, 45–64y, 65–74y, and >74y age categories, respectively. According to the anatomical site, femur NU and humerus NU peak on the age category over 74y, with a prevalence rate of 122 and 59 (per 100,000 person-period) respectively, and tibia NU peaks in the age category 45–64y, with a prevalence rate of 43 per 100,000 person-period. Table 1 describes the cumulative distribution of cases and the prevalence of NU by anatomical site, age category and gender. The prevalence of femur NU in females over 74 years is 4 times-fold that of males over 74, and 5 times-fold the overall prevalence of femur NU in females. Regarding tibia NU, the higher concentration of cases occurred in males from 15 to 64 years, where data doubled the female rates. Finally, female humerus NU rates were 4 times-fold higher than that in males aged over 64 years.

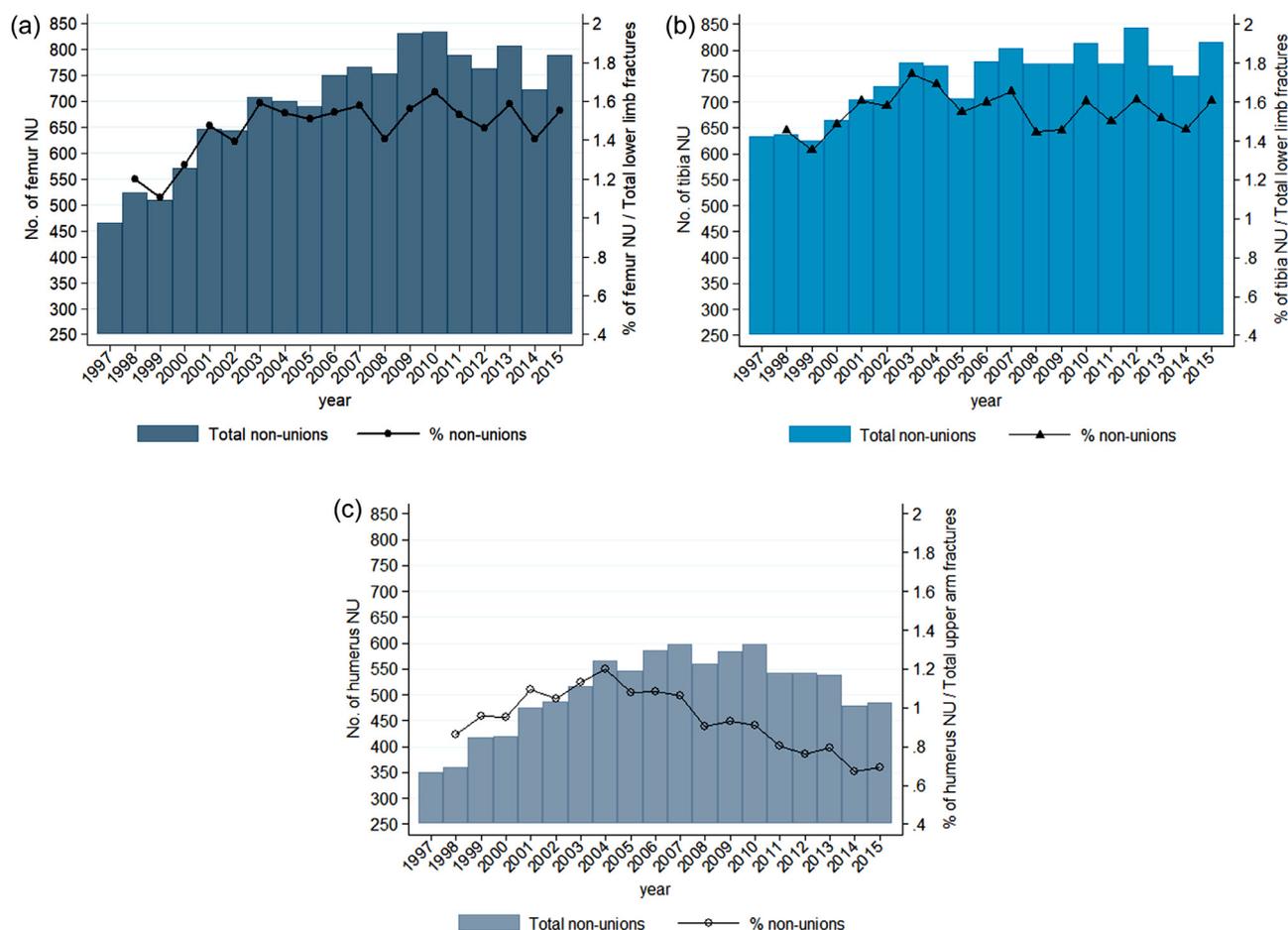


Fig. 1. Number of registered non-unions in Spain (histograms) and percentage of non-unions in the total fractures (frequency polygons), from 1997 to 2015. a) Femur non-unions. b) Tibia non-unions. c) Humerus non-unions.

Table 1
Distribution of non-unions in Spain by age and gender, cumulative data from 1997 to 2015.

	Population (mean)	Total number of non-unions per anatomical location			Non-union prevalence (100,000 persons-period)		
		Femur	Tibia	Humerus	Femur	Tibia	Humerus
Total Males	21,280,884	6037	9522	3821	28.37	44.74	17.96
Total Females	21,692,675	7231	4619	5823	33.33	21.29	26.84
Total <15y	5742905	253	482	155	4.41	8.39	2.70
Total 15-44y	19310489	3981	7084	2534	20.62	36.68	13.12
Total 45-64y	10543456	2869	4565	2725	27.21	43.30	25.85
Total 65-74y	3875559	2221	1344	2159	57.31	34.68	55.71
Total >74y	3501149	3944	666	2071	112.65	19.02	59.15
Males							
<15y	3,125,207	137	276	113	4.38	8.83	3.62
15-44y	9,864,518	2980	5486	1788	30.21	55.61	18.13
45-64y	5,201,804	1630	2880	1217	31.34	55.37	23.40
65-74y	1,781,982	643	641	444	36.08	35.97	24.92
>74y	1,307,373	647	239	259	49.49	18.28	19.81
Females							
<15y	2,617,698	116	206	42	4.43	7.87	1.60
15-44y	9,445,971	1001	1598	746	10.60	16.92	7.90
45-64y	5,341,652	1239	1685	1508	23.20	31.54	28.23
65-74y	2,093,577	1578	703	1715	75.37	33.58	81.92
>74y	2,193,776	3297	427	1812	150.29	19.46	82.60

The risk estimates (Table 2) of femur NU increased with the age category and were 23% higher in females. In the case of tibia non-unions, males are 27% more likely than females to suffer these, and younger population had higher odds ratio. The risk of humerus NU was 83% higher in females than in males, and the risk duplicates with each age category.

The overall NU prevalence rate in Spain is estimated in 86 cases per 100,000 persons in the period (femur NU 31, tibia NU 33, and 22 in the humerus NU). In Table 3, prevalence in some regions appears higher, but the influence decreases when adjusted by age and gender.

Table 2
Risk estimation of non-unions by age and gender category.

Variables	Femur NUOR (CI,95%)	Tibia NUOR (CI,95%)	Humerus NUOR (CI,95%)
Gender:			
Male	1	1	1
Female	1.23 (1.17-1.28)***	0.83 (0.80-0.87)***	1.83 (1.74-1.92)***
Age category:			
<15y	1	1	1
15-44y	0.83 (0.73 - 0.95)*	0.68 (0.61-0.76)***	0.84 (0.720.99)*
45-64y	1.03 (0.89-1.18)	0.83 (0.74-0.92)**	1.53 (1.30-1.79)***
65-74y	1.87 (1.62-2.15)***	0.51 (0.45-0.57)***	2.58 (2.19-3.03)***
>74y	3.74 (3.25-4.29)***	0.22 (0.19-0.25)***	2.05 (1.74-2.42)***

*p<0.05; **p<0.01;***p<0.001
 NU: non-unions. OR: Odds ratio.
 All logistic models adjust with a prob>chi2 lower than 0.001

Table 3
Distribution of non-union per region in Spain, from 1997 to 2015.

Region of Spain	Population (mean)	Total number of non-unions per anatomical location			Non-union prevalence (100,000 person-period)			Prevalence ratio		
		Femur	Tibia	Humerus	Femur	Tibia	Humerus	Femur	Tibia	Humerus
Andalucía	7,862,816	2,086	2,368	1,667	26.53	30.12	21.20	0.86	0.92	0.94
Aragón	1,219,019	357	331	300	29.29	27.15	24.61	0.95	0.83	1.10
Asturias	1,021,824	316	372	222	30.93	36.41	21.73	1.00	1.11	0.97
Baleares	933,610	257	305	220	27.53	32.67	23.56	0.89	0.99	1.05
Canarias	1,798,174	308	381	280	17.13	21.19	15.57	0.55	0.64	0.69
Cantabria	510,942	239	292	133	46.78	57.15	26.03	1.52	1.74	1.16
Castilla y León	1,827,018	564	605	427	33.11	30.87	23.37	1.00	1.01	1.04
Castilla-La Mancha	2,456,603	638	544	421	25.97	22.14	17.14	0.84	0.67	0.76
Cataluña	6,951,883	2,921	2,980	1,942	42.02	42.87	27.93	1.36	1.30	1.24
Comunidad Valenciana	4,596,675	1,224	1,373	1,010	26.63	29.87	21.97	0.86	0.91	0.98
Extremadura	1,004,036	272	301	198	27.09	29.98	19.72	0.88	0.91	0.88
Galicia	2,675,169	736	841	437	27.51	31.44	16.34	0.89	0.96	0.73
Madrid	5,934,491	2,125	2,052	1,359	35.81	34.58	22.90	1.16	1.05	1.02
Murcia	1,236,173	405	396	249	32.76	32.03	20.14	1.06	0.97	0.90
Navarra	543,680	166	237	158	30.53	43.59	29.06	0.99	1.32	1.29
País Vasco	2,089,915	549	659	532	26.27	31.53	25.46	0.85	0.96	1.13
La Rioja	253,173	82	79	68	32.39	31.20	26.86	1.05	0.95	1.20
Ceuta	36,529	8	12	14	21.90	32.85	38.33	0.71	1.00	1.71
Melilla	21,830	15	13	7	68.71	59.55	32.07	2.23	1.81	1.43
SPAIN	42,973,559	13,268	14,141	9,644	30.87	32.91	22.44			

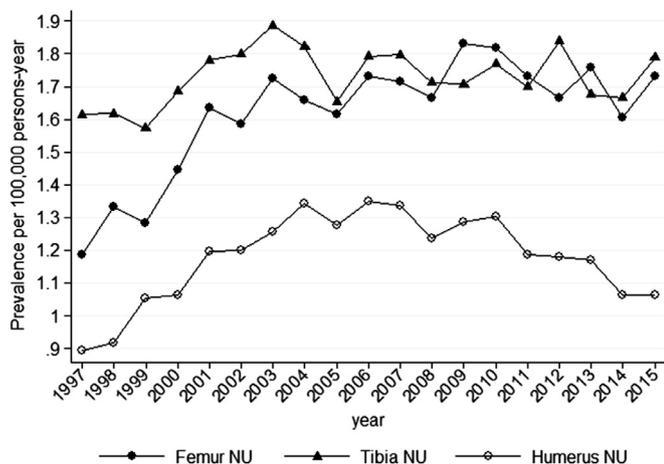


Fig. 2. Annual prevalence rate of long bone non-unions per affected bone (femur, tibia, humerus) in Spain, from 1997 to 2015.

Discussion

The overall proportion of long bone fractures that failed to consolidate and derived into a non-union in Spain, between 1997 and 2015, was 1.4% for the femur, 1.5% for the tibia, and 1% for the

humerus, far from the 5% to 10% that has been generally estimated but does not arise from clear data sources. Besides, our data are close to those results found in recent reports from other regions. [1] When considering readmissions for fracture healing complications, [2] the reported rate is higher, but repeated admissions may be also included. Up to 2.5% of the fractures derived into a non-union in a large Medicare population in a different report, [11] but aged patients with significant co-morbidities may express different non-union rates than the global population, at higher risk for non-union after adjusting for confounders. [2]

The mean annual prevalence of 4.5 per 100,000 person-years in our study is lower than other reports [12] that addressed an incidence of 7.68 per 100,000 person-years. We used the prevalence instead of incidence because we cannot identify the sequence of events in our cases and cannot adjust by mortality, as the population is defined per year. However, our population is defined by national official data and we do not risk to underestimate the denominator, as found in other studies [1].

In our data, the rate of long bone non-union is stable, since 2000 to the last available data in 2015. The tendency of the femur and tibia non-unions looks constant, while the humerus non-union tendency is slowly decreasing, from a rate of 1.3 in 2006 to a rate of 1 in 2015.

Age has been evaluated as an epidemiological risk factor for non-unions but non-union rate has been shown to decrease with age, even in Medicare population where non-union patients were

younger than those that healed normally [11]. Fracture non-union cannot be isolated from fracture severity, fracture location, and disease comorbidities, and therefore age alone is probably not influencing bone healing prognosis, as suggested in epidemiological studies and further proven in matched pair studies [13]. In our study, age over 74 showed more femur NU than other age categories, particularly females, but also humerus NU are more frequent above 65 years of age (Table 1). This increased prevalence is not so evident when adjusted by gender. Therefore, we may consider that the Spanish population structure (with high number of elderly females) may affect this high prevalence, particularly in the femur in concordance with the Scottish cohort. [12] The fracture site is therefore determinant for the variable non-union rate, and different studies confirm this influence [1,11]. Male gender has been identified as a risk factor for non-union in several studies, [1] but this effect was only evident in our tibia NU data, which is probably due to the concentration of high impact injuries, treated in public hospitals in the examined database. Severe trauma, such as motor vehicle accidents, has previously shown increased odds for fracture healing complications [9].

Mills et al. [1] suggested that data from ICD-9 coding may over- or underestimate the rate of non-unions. We also consider that some limitations of this study relate to these potential variations due to coding. In such a broad, nation-wide epidemiological overview, we are restricted by the available data collection system, and granularity is scarce. In Spain from 1997 to 2000, the coding implementation has affected the reporting, and at least for these four years, the rates are underestimated. Also, there are other weaknesses in the methodology of this study. Data include non-unions upon hospital discharge, so ambulatory cases are not recovered (probably scarce) but also repeated admissions may occur for a single case. An overestimation of femur NU, specifically in older females, may have occurred as subtrochanteric fractures may have been included when considering long bone non-union. Besides, we discarded those cases containing a non-union coding and a hip replacement procedure. The use of the ICD-9 codification also has been debatable, but some claimed an accuracy of 95%. [14] Instead, other authors support the use of ICD-10 with an even higher accuracy despite limited anatomical subsets. [1] Of note, this may be highly dependent on the specific size and configuration of the database, in our case dealing with more than 37,000 non-unions from nation-wide collected data, which is currently not validated with ICD-10. Anyway, many specific aspects may not be addressed by secondary database exploitation. Treatment modality may vary in different fracture location, and this can be seen as a study limitation in our setting. Certainly, there is a need of well-powered, well-designed large studies to identify preventable risk factors and resource consumption [2,7,9] and to test the strength of some associations in a particular scenario or a given country with population and healthcare specificities.

Conclusions

This description of the epidemiology of long bone non-unions in Spain confirms that the overall non-union rate has been stable from 2000 to 2015, higher in the tibia and in the femur, compared to the humerus, occurring more frequently in aged females than in males in the femur and the humerus, while the tibia non-unions were more frequent in males and younger age.

Declaration of Competing Interest

The authors confirm that there are no known conflicts of interest associated with this publication and there has been no significant financial support for this work that could have influenced its outcome.

CRediT authorship contribution statement

Norma G. Padilla-Eguiluz: Writing - review & editing, Formal analysis, Data curation, Supervision. **Enrique Gómez-Barrena:** Writing - review & editing, Data curation, Supervision.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at [doi:10.1016/j.injury.2021.02.053](https://doi.org/10.1016/j.injury.2021.02.053).

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