Injury 50 (2019) 2196–2202

Contents lists available at ScienceDirect

Injury

journal homepage: www.elsevier.com/locate/injury

Sonographic bridging callus: An early predictor of fracture union

J.A. Nicholson*, W.M. Oliver, J. LizHang, T. MacGillivray, F. Perks, C.M. Robinson, A.H.R. Simpson

Department of Orthopaedic and Trauma Surgery, Edinburgh Royal Infirmary, Little France, Edinburgh EH16 4SU, United Kingdom

ARTICLE INFO

Article history:
Accepted 19 September 2019

Keywords:
Ultrasound
Sonographic bridging callus
Nonunion prediction

ABSTRACT

Background: There is currently a lack of agreed criteria for sonographic assessment of callus and reliability between reviewers.

The primary aim of this study was to determine criteria and reviewer agreement for sonographic bridging callus (SBC) on ultrasound. The secondary aim was to analyse the use of ultrasound to detect bridging callus in a prospective cohort of patients with a conservatively managed clavicle fracture.

Methods: A prospective cohort of conservatively managed displaced midshaft clavicle fractures underwent ultrasound scanning at three-, six- and 12-weeks post-injury. The main outcome was nonunion confirmed at six months on CT scanning. Five patients with confirmed nonunion were compared against a control group of 15 patients with timely union at three months.

The ultrasound scans were interpreted by two blinded reviewers to evaluate sonographic callus features with agreement determined by weighted kappa. A further validation study was undertaken by four blinded reviewers using the intraclass-correlation-coefficient (ICC) using the most clinically relevant findings of the pilot work.

Results: At three weeks post-injury fibrocartilaginous material was present in 80% of patients (16/20). When detected this was associated with union (sensitivity 93%, specificity 60%, $p = 0.03$) with the inter-observer agreement rated 'fair' on kappa (0.44).

At six weeks only 10% (2/20) of patients had bridging callus on radiograph but 60% (12/20) had sonographic bridging callus (SBC) and when present all united (sensitivity 80%, specificity 100%, $p = 0.002$). At 12 weeks, bridging callus was present on both radiographs and ultrasound in all patients that united ($n = 15$, sensitivity 100%, specificity 100%, $p < 0.001$). No patient that developed a nonunion at six months post-injury had SBC at any time point. At six-weeks the absence of SBC had a positive predictive value for nonunion of 63% of patients (5/8) and by 12 weeks it was 100% (5/5).

The SBC detection rated 'very strong' for intra- (kappa 0.92) and inter-observer agreement (kappa 0.84). The ICC of SBC at six-weeks with four blinded reviewers was 0.82 (95% confidence interval 0.68–0.91).

Conclusions: This is the first study to establish time specific ultrasound fracture findings with a repeatable technique and assess the agreement between blinded reviewers.

Background

Nonunion is associated with considerable patient morbidity and increased medical costs. The ability to predict union of fractures is challenging. Despite the widespread use of radiographs, the ability to detect bridging callus in skeletally mature adults in the first six weeks following injury is unreliable in long bone fractures and agreement between observers is often poor [1-4]. Use of computed tomography (CT) to accurately determine fracture union is increasing, but this requires a substantial radiation dose and detection of bridging callus is visualized at a similar time scale to radiographs [5,6].

Over the past two decades the potential role of ultrasound to detect unmineralized callus prior to radiographs has been proposed by several independent research groups [1,7–12]. Most papers describe a sequence of evolving callus at the fracture site represented by a hyperechoic (white) signal that bridges the fracture ends. This is consistently detected prior to the appearance of callus on radiographs from as early as 2–6 weeks post-injury. Evaluating the fracture using different 'windows' allows for a three-dimensional assessment of callus configuration in real time [13]. This could have implications for confirming union and identifying those at high risk of delayed union in long bone fractures following

* Corresponding author.
E-mail address: jamienicholson@nhs.net (J.A. Nicholson).

https://doi.org/10.1016/j.injury.2019.09.027
0020-1383/

both conservative and operative management (e.g. tibia, humerus, ulnar and clavicle).

Despite work on early callus identification, ultrasound is not routinely used in clinical practice and further research in this area has been limited in recent years [14]. One of the main limitations is orthopaedic surgeons' unfamiliarity with ultrasound and the absence of specific agreed criteria for ultrasound interpretation of callus. What constitutes sonographic detected callus lacks a clear description and agreement between observers has not been previously explored. Secondly, if ultrasound does have the ability to detect bridging callus reliably prior to plain radiographs, this requires further validation in the clinical setting to assess whether this translates into the early prediction of confirming union and identifying those at high risk of delayed union.

Aims and objectives

- The primary aim of this study was to determine objective interpretation criteria and reviewer agreement callus on ultrasound.
- The secondary aim was to analyse the use of ultrasound to detect bridging callus in a prospective cohort of patients with a conservatively managed clavicle fracture to determine if ultrasound could predict union earlier to conventional radiographs.

Methods

Study participants and study protocol

A prospective cohort of patients with conservatively managed displaced midshaft clavicle fractures were recruited at their first clinic presentation. At each appointment (3, 6 and 12 weeks) a plain anteroposterior radiograph was performed with an ultrasound scan of the fracture site. If there was persistent pain or absence of bridging callus on the radiograph at six months post-injury, patients underwent a CT scan to confirm nonunion and were offered fixation. From this cohort the first five nonunion patients were selected, along with a control group of 15 patients that united in a timely fashion with clear bridging callus on the three-month radiograph. Ethical approval for the use of ultrasound to observe fracture healing was prospectively obtained from the local Research Ethics Committee (reference number 06/S1103/51).

Ultrasound B-mode imaging and scanning protocol

Patients underwent a standardised ultrasound scan performed by an Orthopaedic surgeon with training in ultrasound. The TA Sonix L14-5 MHz/38 mm ultrasound probe (BK Medical North, America) was used and set to 3–7 MHz and calibrated to 6 cm depth, a standard setting for most superficial musculoskeletal ultrasound evaluations.

The fracture site was imaged in both the long and short axis moving slowly at approximately 5–10 mm per second with real time capture of frames for multiple slices over the site of interest. At the fracture site the probe was carefully rocked, tilted and rotated to ensure perpendicular visualisation of callus and avoid anisotropy which may produce a false anechoic signal (loss of signal).

Most displaced clavicle fractures have a medial fragment which is superiorly displaced due to the trapezoid and sternoclavicular muscles, and a lateral fragment that is inferior due to pectoralis major and weight of the upper limb girdle. The long axis gave a familiar view of the fracture site similar to a radiograph and could evaluate the superior, anterior and posterior cortical edges of the fracture depending on probe orientation. The short axis gives a cross-section of the bone similar to a sagittal slice on CT of the clavicle. This can be useful if the fracture site is distorted by acoustic shadow on the long axis and to confirm or refute the presence of bridging callus. Like the long axis view, this gives an excellent view of the superior, anterior and posterior surface of the clavicle, but the inferior surface is invariably lost due to acoustic shadow (Fig. 1).

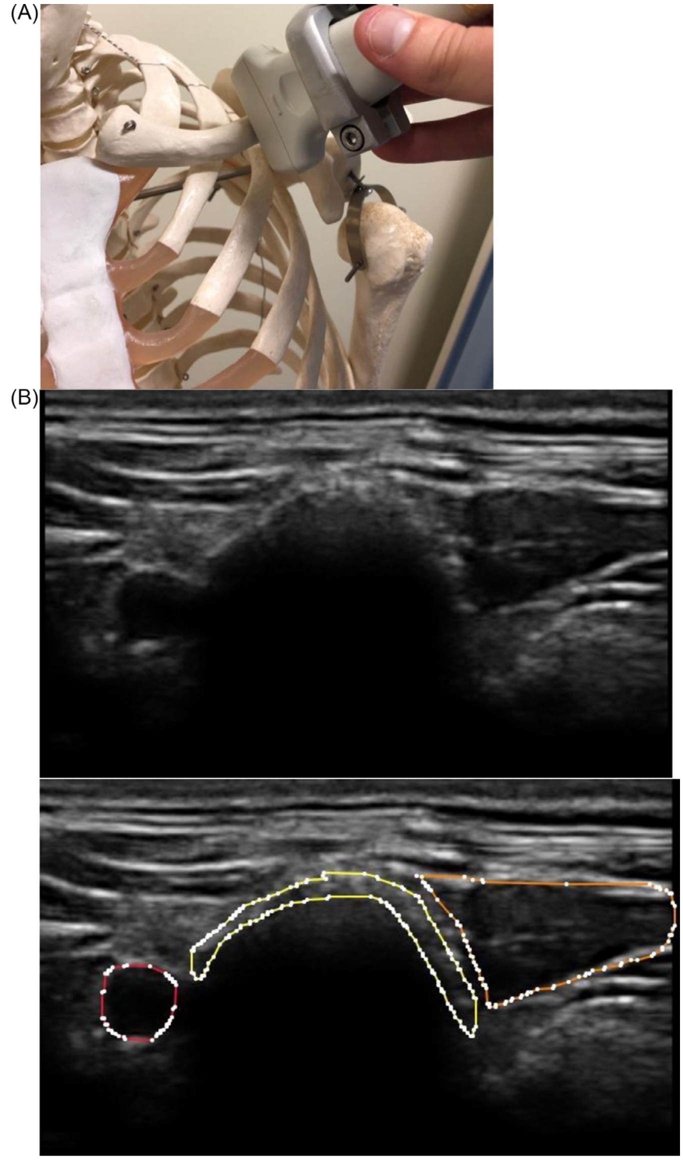


Fig. 1. (A) Demonstration of short axis ultrasound evaluation of the clavicle. (B) Ultrasound image with the cross section anatomy defined. Subclavian vein posterior to clavicle (red). Superior cortical surface of the clavicle (yellow). Pectoralis major muscle anterior to the clavicle (orange). (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

Callus detection on ultrasound and radiographs

To determine the acoustic properties of callus a discussion took place between the authors which included orthopaedic surgeons, a musculoskeletal radiologist and an imaging physicist, based on the existing literature and previous pilot work in the department. Long and short axis ultrasound scanning enabled several different orientations of the fracture site, and it was agreed that callus detection should take place on both the long axis and short axis to limit the artefact from acoustic shadow.

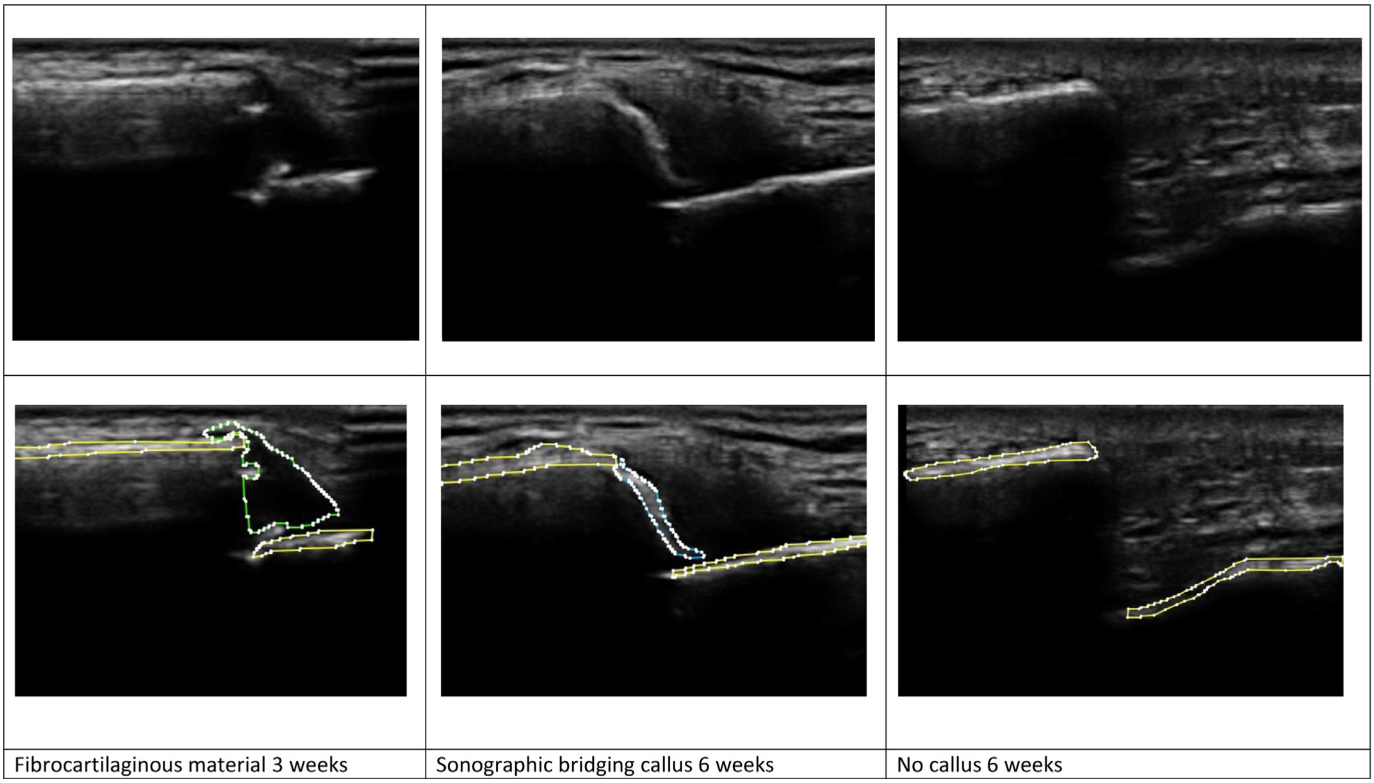


Fig. 2. Callus appearance on ultrasound, showing intact bone cortices (yellow), fibrocartilaginous material (green) and sonographic bridging callus (blue). (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

Ultrasound interpretation at the fracture site was considered as one of three distinct entities; no callus, fibrocartilaginous material or sonographic bridging callus (SBC) (Fig. 2). No callus meant there was no change at the fracture compared to that of the surrounding soft tissue envelope. Early fibrocartilaginous material (e.g. mesenchymal callus) was defined as hypoechoic homogenous signal extending between the fracture out with the cortical surface of each of the respective bone ends. SBC was defined as a linear hyperechoic signal, with a similar echo intensity (EI) to that of the cortical bone, bridging the fracture ends. To avoid confusion with fracture comminution, a complete unbroken view of SBC was required between the fracture fragments on either the anterior, superior or posterior cortices without any obvious gapping. For segmental fractures this was required at both fracture sites.

Detection of bridging callus on radiographs was graded prospectively and based solely on the standard anteroposterior radiograph. Bridging callus required an unbroken cortical line extending between the medial and lateral fragment. When comminution was present the bridging callus needed to be present across all fracture lines otherwise the callus was considered non-bridging. Given that a clavicle fracture line can usually be visualised for several months post-injury, the presence of the fracture line itself did not affect assessment provided the line did not extend into the callus.

Identifying tissue with greyscale echo intensity

EI can be used to discriminate between tissues and is well-established in musculoskeletal ultrasound for identifying muscle pathology with good repeatability [15,16]. It is unknown if the EI provides information on the developing callus or the early prediction of delayed union. On B-mode (or brightness mode) the EI is visualised as a greyscale value of individual pixels in a defined region of interest. This is typically processed from 0 (black) to 255 (white). A low EI represents less reflectance (therefore low acoustic impedance) with a resultant dark (hypoechoic) image, whereas a high EI represents greater reflectance and a bright image (hyperechoic).

A total of 60 patient scans were available from the study cohort (20 patients from 3 different time intervals). From these the EI of the fibrocartilaginous material and sonographic callus (bridging or non-bridging) was estimated. Five estimates of the EI area of interest were determined from independent image slices. Imaging interpretation was performed using Stradwin (Cambridge University Engineering Department, UK). This allows a predefined area of interest to be selected and a mean EI taken from this. All measurements were performed by the first author blinded to the patient outcome.

Reviewer agreement and statistics

Statistical analysis was performed using SPSS version 24 (IBM, Chicago, IL, USA). Data was tested for normal distribution with the D'Agostino and Pearson test. Linear variables (EI data) were assessed using the independent- Student *t*-test for parametric data or the Mann–Whitney *U* test for nonparametric data. ANOVA was used to compare the mean EI of over two mean variables. Differences between dichotomous data were assessed using the Chi-square test. A *p*-value of < 0.05 was defined as statistically significant.

To determine the agreement of callus interpretation, a pilot of 30 ultrasound scans were reviewed by two observers, both of whom were Orthopaedic surgeons with training in performing and interpreting ultrasound for the purpose of fracture evaluation as described above. Both reviewers were blinded to the outcome of the cases (i.e. union or nonunion) and reviewed the ultrasound and radiographs independently. The first author completed a second series of blinded observations with a minimum of 72 h sepa-

Table 1
Echo intensity (EI) of cortical bone, fibrocartilaginous material and hard callus at three time-points. Results shown as mean (95% confidence interval). Significance $p < 0.05^*$.

	Echo Intensity (EI)			
	3 week	6 week	12 week	*p*-value
Cortical Bone	126.9 (129.8–144.1)	137.8 (133.8–141.7)	137.5 (131.8–143.2)	0.904
Fibrocartilaginous	10.6 (8.6–12.6)	10.0 (9.1–10.9)	10.2 (9.1–11.3)	0.078
Bridging Callus	80.6 (71.1–90.1)	87.9 (83.5–92.3)	83.1 (79.0–87.1)	0.169

ration for intra-observer agreement. Weighted kappa was used to determine the strength of association between two observers with 0.4–0.6 fair, 0.6–0.8 strong and 0.8–1.0 close to perfect agreement [17].

A further evaluation of the clinical application and usefulness of the scan interpretation was undertaken using four blinded reviewers including orthopaedic surgeons and radiologists to determine the intraclass-correlation-coefficient (ICC). The scan timing and callus findings that proved most useful from the pilot data was used. A two-way mixed model, with assessment of consistency between observers was used to calculate a 'single measures' ICC.

Results

The mean age of patients was 40.3 (95% confidence interval (CI) 33.2–47.4), there were 11 men (55%) and 5 were smokers (25%). Those with a nonunion were more likely to be smokers ($p = 0.04$). All patients tolerated the ultrasound scanning without difficulty and the fracture site was visualized in all cases to allow interpretation as planned.

Definition of tissue and echo intensity

The surface of the cortical bone was easily defined as a thin linear structure with a uniform hyperechoic surface and a dense acoustic shadow cast deep to it. There was a wide variation in EI, with a mean of 137.5 (SD 19.2, 95% CI 134.6–140.5) (Table 1).

Fibrocartilaginous material was identifiable as an irregular, homogenous, hypoechoic signal extending above the periosteal cortical surface of the bone at the fracture site. It was visualised in the majority of patients at three weeks post-injury (16/20). The EI was a mean of 10.2 (SD 4.2, 95% CI 9.5–10.8). There was no difference in the EI at any of the three time-points (ANOVA, $p = 0.08$). There was no difference in the fibrocartilaginous material EI in patients with union versus nonunion ($p = 0.17$).

The SBC had a clear hyperechoic, homogenous, linear border which formed near the surface of the fibrocartilaginous material between the fracture ends. Although no complete SBC was observed until six weeks, non-bridging sonographic callus at three weeks allowed EI estimates. The EI of the callus was below that of the cortical bone but clearly identifiable from the surrounding soft tissue envelope with a mean of 85.0 (SD 19.1, 95% CI 82.1–88.0). No difference was observed between the three-, six- and 12-week EI (ANOVA $p = 0.17$) or the appearance in patients with union versus nonunion ($p = 0.30$).

Fibrocartilaginous material

Sonographic fibrocartilaginous material was more likely to be seen at three weeks in those who went onto union with a sensitivity of 93.3% and specificity of 60% ($p = 0.03$) (Table 2). At six weeks this improved to 100% sensitivity to determine union but only 40% specificity as patients which ultimately developed a nonunion also had evidence of fibrocartilaginous material by this time point ($p = 0.05$). At 12 weeks the fibrocartilaginous material began to disappear with remodelling of the hyperechoic SBC as union occurred and it was not useful at this time point to distinguish between union and nonunion patients ($p = 0.29$).

Table 2
Demographics and clinical information of nonunion versus delayed union. 95% confidence interval (CI) shown in brackets. Significance <0.05*.

Parameter	Union $n = 15$	Nonunion $n = 5$	*p*-value
Age (years)	36.9 (29.3–44.5)	50.4 (30.7–70.1)	0.08
Male/Female	8/7	3/2	0.795
Smoker	13.3% (2/15)	60% (3/5)	0.037*
Simple/Comminution	10/5	3/2	0.787
Fibrocartilaginous			
3 week	14/15	2/5	0.032*
6 week	15/15	3/5	0.05*
12 week	10/15	2/5	0.292
Sonographic bridging callus			
3 week	0/15	0/15	1.0
6 week	12/15	0/15	0.002*
12 week	15/15	0/5	<0.001*
Radiographic callus			
3 week	0/15	0/15	1.0
6 week	2/15	0/15	0.389
12 week	15/15	0/15	<0.001*

Kappa agreement for the detection of fibrocartilaginous material was 'fair' for intra- (0.55, $p = 0.002$, CI 0.24–0.87) and inter-observer (0.44, $p = 0.008$, CI 0.12–0.77) error which reflected the difficulty with interpretation mostly due to the acoustic shadow from cortical bone. Comminution ($p = 0.38$) did not significantly influence kappa agreement.

Sonographic bridging callus detection

At six weeks SBC was evident in 60% of patients (12/20) and when present all achieved union (sensitivity 80% and specificity 100% for union ($p = 0.002$)). Of the eight patients without bridging callus, five went onto nonunion (positive predictive value for nonunion 63%, $p = 0.001$)(Clinical examples Figs. 3 and 4). Of the five smokers in the study, none displayed SBC at six weeks ($p = 0.002$), three of which ultimately developed a nonunion. Age, comminution and gender did not affect presence of bridging callus. At twelve weeks 100% of those who united displayed SBC and none in those who developed a nonunion (sensitivity 100% and specificity 100%, $p < 0.001$).

The weighted kappa indicated very strong agreement for SBC interpretation for both intra- (0.92, $p < 0.001$, CI 0.76–1.08) and inter-observer error (0.82, $p < 0.001$, CI 0.63–1.05). There was less difficulty with interpretation of the linear hyperechoic bridging hard callus between reviewers, and the risk of anisotropy was minimised by multiple image captures over the fracture site. Agreement was not affected by fracture comminution ($p = 0.39$).

At six weeks 90% (18/20) of patients had some callus evident on radiograph but this was not significantly different between union and nonunion ($p = 0.74$). Bridging callus was evident in only two patients at six weeks, when present union occurred ($p = 0.39$). By 12 weeks, 100% of patients that united had bridging callus, conversely none was found in those who developed a nonunion ($p < 0.001$) in keeping with the ultrasound findings. Agreement

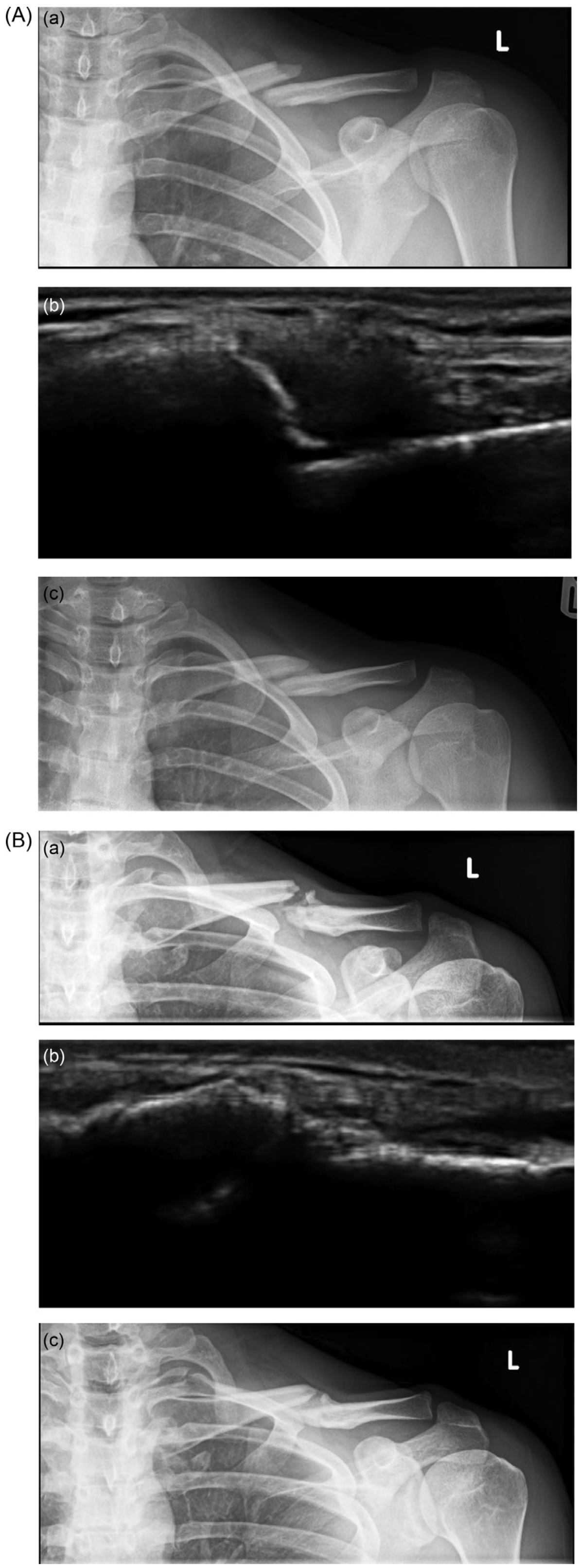
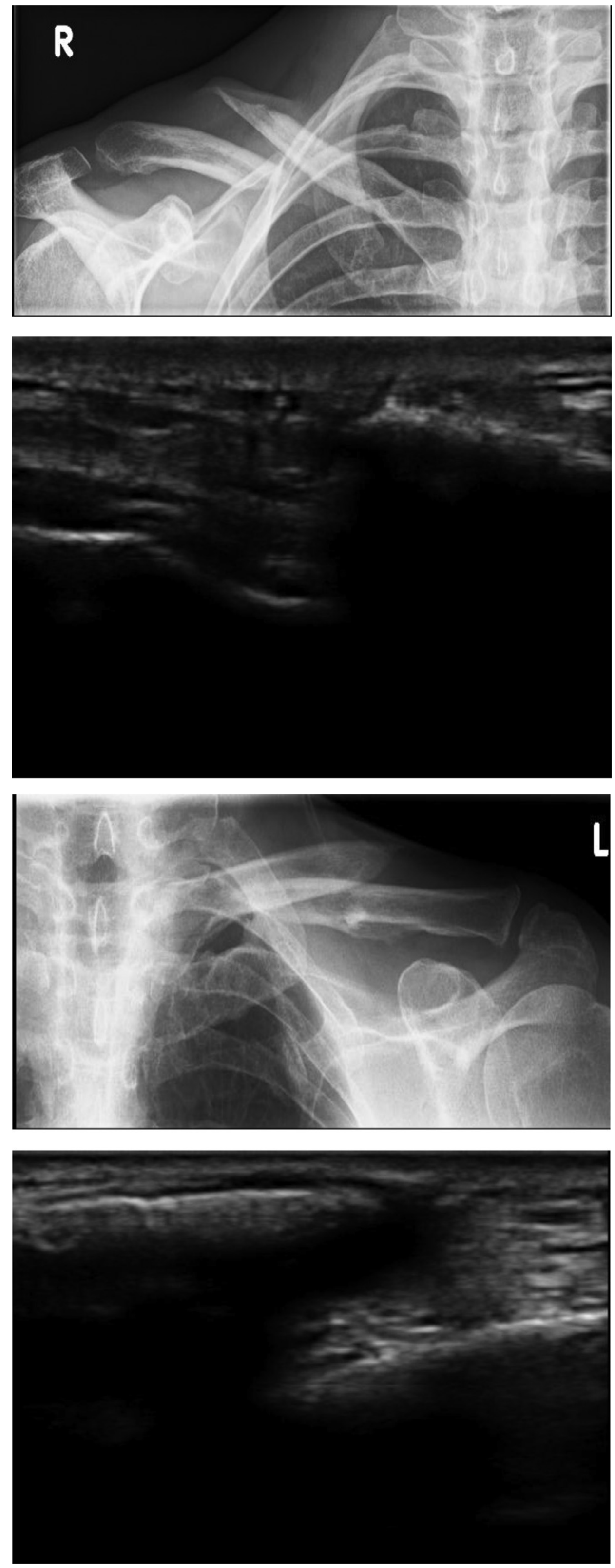


Fig. 3. Two patients with early bridging callus detection on ultrasound.
(A)(a-c) 6-week radiograph. 6-week ultrasound. 12-week radiograph.
(B)(a-c) 6-week radiograph. 6-week ultrasound. 12-week radiograph.



Figs. 4. Two patients with nonunion with absent bridging callus.
(A)(a-b) 6-week radiograph. 6-week ultrasound.
(B)(a-b) 6-week radiograph. 6-week ultrasound.

was excellent for intra- (0.84. $p < 0.001$, CI 0.53–1.15) and strong for inter-observer agreement (0.71, $p < 0.001$, CI 0.34–1.08).

Intra class correlation between multiple reviewers

The six week detection of SBC proved to be the most clinically applicable and reproducible ultrasound finding from the initial pilot work. This observation was further validated with four blinded reviewers. The twenty blinded scans produced an ICC of 0.82 (CI 0.68–0.91) between four observers giving an excellent agreement on the presence of SBC.

Discussion

Ultrasound evaluation of fracture healing has distinctive findings which may allow the early identification of bone union and prediction of patients at risk of delayed union. Although fibrocartilaginous material could be visualized at three weeks, SBC at six weeks had superior reviewer agreement and a higher degree of accuracy for predicting union with 100% specificity when present. Agreement between blinded reviewers for SBC assessment was comparable to that of radiographs and preceded the radiographic findings by six weeks in the majority of patients.

Distinguishing between tissue on B-mode imaging is based on the echogenicity of tissue which is dependent on the acoustic impedance (AI). Bone has the greatest acoustic impedance (6.47×10^6 kg m^{-2} s^{-1}) followed by cartilage (2.12×10^6) haematoma (1.67×10^6) and fat (1.33×10^6) [18,19]. Given the high attenuation of ultrasound in bone, a strong acoustic shadow is cast beyond the near cortex meaning assessment of deeper structures including the far cortices is not possible.

A fracture causes a linear uniform break in the hyperechoic surface of the cortical bone and is easily identifiable [20]. Early fibrocartilaginous callus on the periosteal surface appears to have a similar appearance to articular cartilage which has a uniform homogenous hypoechoic structure (dark appearance) due to ultrasound wave absorption but little reflection [19,20]. Maturing callus is thought to have an increasingly dense hyperechoic boundary as it calcifies and reconstitutes into cortical bone. These appearances do not appear to be based on dense mineralization as required for traditional radiographs and are detectable earlier with ultrasound. Detection and interpretation of non-bridging callus by reviewers was deemed likely to vary widely and was therefore considered to be of less clinical application. Anisotropy can affect the SBC interpretation as bridging callus (white signal) could be missed if the ultrasound probe is not directed perpendicular to the site of interest thereby giving a false anechoic signal (black signal). This is akin to evaluations in the shoulder where a tendon tear is falsely interpreted due to loss of signal by anisotropy. Once the fracture site is located, this can be minimised by holding the ultrasound probe in the same position and gently altering the beam direction to ensure perpendicular image capture.

The ability to form bridging callus across a fracture site is thought to be a crucial event for the reduction of strain, and thereby promoting union in keeping with Perren's strain theory [21–23]. It is known that objective grading criteria of radiographs to estimate bridging callus is strongly associated with union for the tibia [3] and more recently the hip [24]. The main limitation with radiographic callus detection is the time required to visualise it, usually at the 10–12 week mark [3,25]. This markedly reduces the utility of radiographs to identifying potential delayed union of fractures within the first three months of injury.

Ultrasound was first used for fracture identification in 1988 for the diagnosis of neonatal clavicle fractures [26]. It has been subsequently shown to be useful in diagnosis of a range of common paediatric fractures [27-29], adult rib fractures [30], stress fractures [31] and long bone fractures in the resuscitation setting [32]. The ability to detect callus formation prior to radiographs was demonstrated following distraction osteogenesis in 1990 [1].

Subsequent research has shown the ability of ultrasound to detect callus formation at approximately three weeks following fracture [10,33]. Increasing hyperechoic callus formation at the fracture site is universally described, with bridging bone eventually obscuring the fracture site or intra-medullary canal following tibial nailing [34]. The ability to identify patients at risk of a delayed union following intramedullary nailing of the tibia was demonstrated by Moed et al. who found that ultrasound allowed early intervention at three months [13]. This was replicated with a more recent study showing nonunion was identified at 18 weeks on ultrasound versus 26 weeks on plain radiographs [14].

The main limitation with ultrasound studies to date is the lack of agreed objective criteria for callus interpretation, reviewer agreement and finally the accuracy of callus interpretation in ultimately predicting clinical union. Our findings suggest that SBC had superior intra- and inter-observer reliability over early sonographic detected fibrocartilaginous material periosteal reaction. The validation study with several blinded reviewers showed excellent ICC indicating strong agreement. All scans were blinded by unique coding to ensure reviewers were not biased by the union status or timing of the scan. No study to our knowledge explored reviewer agreement of bridging callus on ultrasound. The EI evaluation of callus was not found to be useful for the prediction of union.

Our cohort of clavicle fractures provided a homogenous sample for callus evaluation. Early prediction of clavicle nonunion would be advantageous given increasing evidence that outcome following conservative management is equivalent to acute fixation if timely union occurs [35–39]. Nonunion development is influenced by smoking, increasing age, fracture displacement [40,41], and lack of clinical recovery [42]. However, these lack specificity and do not accurately predict risk for an individual. SBC was present at six weeks in the majority of those who united and was absent in all those who went on to nonunion, giving an excellent sensitivity of 80% and a specificity of 100% for union prediction. The interpretation of ultrasound had similar agreement to radiographs but detection of bridging callus on radiographs took twice as long to visualize at three months. Modelling this to specific patient risk factors or delayed clinical recovery with functional scoring in a larger cohort may yield more specific findings.

All scans in this study were undertaken by one Orthopaedic surgeon with basic ultrasound training. The ultrasound frequency and depth of signal settings reflected standard settings used for visualisation of superficial structure in musculoskeletal ultrasound and were not adjusted. In this study we observed a short learning curve for ultrasound scanning, which principally requires attention at the fracture site to ensure several images are acquired with alternating ('rocking') orientation of the probe to ensure perpendicular visualisation of callus to avoid loss of signal and anisotropy. It would be possible to request such information from a radiologist; however we found the scan technique easy to acquire with minimal training. Fractures with marked tenting of the skin can result in temporary loss of signal but in all cases in our series we were able to visualise the fracture site sufficiently to make a judgement. We selected a cohort of patients with early clinical and radiological union at three months for our control group. Our findings require validation in a larger cohort of diaphyseal fractures to establish the accuracy of ultrasound scans in predicting nonunion.

Conclusions

The ability to monitor diaphyseal fracture healing with ultrasound may have practical implications for early identification of patients at high risk of nonunion. Evaluation of SBC at six weeks has excellent accuracy to predict union with strong reviewer agreement. This is the first study to establish time specific ultrasound fracture findings with a repeatable technique and assess the agreement between blinded reviewers.

Declaration of Competing Interest

There are no conflicts of interest to declare for any of the authors involved in this study.

References

[1] Young JW, Kostrubiak IS, Resnik CS, Paley D. Sonographic evaluation of bone production at the distraction site in Ilizarov limb-lengthening procedures. Am J Roentgenol. American Public Health Association 1990;154(Jan (1)):125–8.

[2] Cook GE, Bates BD, Tornetta P, Mckee MD, Morshed S, Slobogean GP, et al. Assessment of fracture repair. J Orthop Trauma 2015;29(Dec):S57–61.

[3] Leow JM, Clement ND, Tawonsawatruk T, Simpson CJ, Simpson AHRW. The radiographic union scale in tibial (RUST) fractures. Bone Joint Res 2016;5(Apr (4)):116–21.

[4] DiSilvio F Jr, Foyil S, Schiffman B, Bernstein M, Summers H, Lack WD. Long bone union accurately predicted by cortical bridging within 4 months. JBJS Open Access 2018;3(Dec (4)):e0012.

[5] Grigoryan M, Lynch JA, Fierlinger AL, Guermazi A, Fan B, MacLean DB, et al. Quantitative and qualitative assessment of closed fracture healing using computed tomography and conventional radiography. Acad Radiol 2003;10(Nov (11)):1267–73.

[6] Krestan CR, Noske H, Vasilevska V, Weber M, Schueller G, Imhof H, et al. MDCT versus digital radiography in the evaluation of bone healing in orthopedic patients. Am J Roentgenol 2006;186(Jun (6)):1754–60.

[7] Derbyshire ND, Simpson AH. A role for ultrasound in limb lengthening. Br J Radiol 1992;65(Jul (775)):576–80.

[8] Eyres KS, Bell MJ, Kanis JA. Methods of assessing new bone formation during limb lengthening. Ultrasonography, dual energy X-ray absorptiometry and radiography compared. J Bone Joint Surg Br 1993;75(May (3)):358–64.

[9] Craig JG, Jacobson JA, Moed BR. Ultrasound of fracture and bone healing. Radiol Clin North Am 1999;37(Jul (4)):737–51 –ix.

[10] Ricciardi L, Perissinotto A, Dabala M. Mechanical monitoring of fracture healing using ultrasound imaging. Clin Orthop Relat Res 1993;293(Aug):71–6.

[11] Malde HM, Hemmadi SS, Chadda D, Parihar ML, Bhosale PB, Kedar RP. The role of skeletal sonography in limb lengthening procedures. J Postgrad Med. Medknow Publications 1993;39(Jul (3)):127–9.

[12] Wawrzyk M, Sokal J, Andrzejewska E, Przewratil P. The role of ultrasound imaging of callus formation in the treatment of long bone fractures in children. Pol J Radiol 2015;80:473–8.

[13] Moed BR, Subramanian S, van Holsbeeck M, Watson JT, Cramer KE, Karges DE, et al. Ultrasound for the early diagnosis of Tibial fracture healing after static interlocked nailing without reaming: clinical results. J Orthop Trauma 1998;12(Mar (3)):206–13.

[14] Chachan S, Tudu B, Sahu B. Ultrasound monitoring of fracture healing. J Orthop Trauma 2015;29(Mar (3)):e133–8.

[15] Pillen S, Tak RO, Zwarts MJ, Lammens MMY, Verrijp KN, Arts IMP, et al. Skeletal muscle ultrasound: correlation between fibrous tissue and echo intensity. Ultrasound Med Biol 2009;35(Mar (3)):443–6.

[16] Varanoske AN, Fukuda DH, Boone CH, Beyer KS, Stout JR, Hoffman JR. Homogeneity of echo intensity values in transverse ultrasound images. Muscle Nerve 2017;56(Feb (1)):93–8.

[17] Fleiss JL, Levin B, Paik MC. Statistical methods for rates and proportions. Hoboken, NJ, USA: John Wiley & Sons, Inc; 2003.

[18] Hoskins P, Martin K, Thrush A. Diagnostic ultrasound: physics and equipment. Cambridge University Press; 2010.

[19] Leicht S, Raum K. Acoustic impedance changes in cartilage and subchondral bone due to primary arthrosis. Ultrasonics 2008;48(Nov (6–7)):613–20.

[20] Meenagh G, Filippucci E, Kane D, Taggart A, Grassi W. Ultrasonography in rheumatology: developing its potential in clinical practice and research. Rheumatology 2007;46(Jan (1)):3–5.

[21] Perren SM. Evolution of the internal fixation of long bone fractures: the scientific basis of biological internal fixation: choosing a new balance between stability and biology. J Bone Joint Surg Br 2002;84(Nov (8)):1093–110.

[22] Marsell R, Einhorn TA. The biology of fracture healing. Injury 2011;42(Jun (6)):551–5.

[23] Einhorn TA, Gerstenfeld LC. Fracture healing: mechanisms and interventions. Nat Rev Rheumatol 2014;11(Sep (1)):45–54.

[24] Frank T, Osterhoff G, Sprague S, Garibaldi A, Bhandari M, et al. The radiographic union score for hip (RUSH) identifies radiographic nonunion of femoral neck fractures. Clin. Orthop. Relat. Res. 2016;474(Jan (6)):1396–404 Springer US.

[25] Simpson AHRW. The forgotten phase of fracture healing: the need to predict nonunion. Bone Joint Res 2017;6(Oct (10)):610–11.

[26] Katz R, Landman J, Dulitzky F, Bar-Ziv J. Fracture of the clavicle in the newborn. An ultrasound diagnosis. J Ultrasound Med 1988;7(Jan (1)):21–3.

[27] Hübner U, Schlicht W, Outzen S, Barthel M, Halsband H. Ultrasound in the diagnosis of fractures in children. J Bone Joint Surg Br 2000;82(Nov (8)):1170–3.

[28] Williamson D, Watura R, Cobby M. Ultrasound imaging of forearm fractures in children: a viable alternative? J Accid Emerg Med Jan 2000;17(1):22–4 BMJ Publishing Group.

[29] Ackermann O, Liedgens P, Eckert K, Chelangattucherry E, Husain B, Ruchholtz S. Ultrasound diagnosis of forearm fractures in children: a prospective multicenter study. Unfallchirurg 2009;112(Aug (8)):706–11.

[30] Griffith JF, Rainer TH, Ching AS, Law KL, Cocks RA, Metreweli C. Sonography compared with radiography in revealing acute rib fracture. Am J Roentgenol. American Public Health Association 1999;173(Dec (6)):1603–9.

[31] Hoffman DF, Adams E, Bianchi S. Ultrasonography of fractures in sports medicine. Br J Sports Med 2015;49(Feb (3)):152–60.

[32] Marshburn TH, Legome E, Sargsyan A, Li SMJ, Noble VA, Dulchavsky SA, et al. Goal-directed ultrasound in the detection of long-bone fractures. J Trauma 2004;57(Aug (2)):329–32.

[33] N M. Ultrasonographic appearance of external callus in long-bone fractures. Injury. Elsevier 1995;26(Jan (1)):5–12.

[34] Moed BR, Watson JT, Goldschmidt P, van Holsbeeck M. Ultrasound for the early diagnosis of fracture healing after interlocking nailing of the tibia without reaming. Clin. Orthop. Relat. Res. 1995;310(Jan):137–44.

[35] Virtanen KJ, Remes V, Pajarinen J, Savolainen V, Björkenheim J-M, Paavola M. Sling compared with plate osteosynthesis for treatment of displaced midshaft clavicular fractures. J Bone Joint Surg Am 2012;94(Sep (17)):1546–53.

[36] Robinson CM, Goudie EB, Murray IR, Jenkins PJ, Ahktar MA, Read EO, et al. Open reduction and plate fixation versus nonoperative treatment for displaced midshaft clavicular fractures. J Bone Joint Surg Am 2013;95(Sep (17)):1576–84.

[37] Woltz S, Stegeman SA, Krijnen P, van Dijkman BA, van Thiel TPH, Schep NWL, et al. Plate fixation compared with nonoperative treatment for displaced midshaft clavicular fractures: a multicenter randomized controlled trial. J Bone Joint Surg Am 2017;99(Jan (2)):106–12.

[38] Ahrens PM, Garlick NI, Barber J, Tims EMClavicle Trial Collaborative Group. The clavicle trial: a multicenter randomized controlled trial comparing operative with nonoperative treatment of displaced midshaft clavicle fractures. J Bone Joint Surg Am 2017;99(Aug (16)):1345–54.

[39] Qvist AH, Væsel MT, Jensen CM, Jensen SL. Plate fixation compared with nonoperative treatment of displaced midshaft clavicular fractures: a randomized clinical trial. Bone Joint J 2018;100-B(Oct (10)):1385–91.

[40] Liu W, Xiao J, Ji F, Xie Y, Hao Y. Intrinsic and extrinsic risk factors for nonunion after nonoperative treatment of midshaft clavicle fractures. Orthop Traumatol. Elsevier Masson SAS 2015;101(Apr (2)):197–200.

[41] Murray IR, Foster CJ, Eros A, Robinson CM. Risk factors for nonunion after nonoperative treatment of displaced midshaft fractures of the clavicle. J Bone Joint Surg Am 2013;95(Jul (13)):1153–8.

[42] Clement ND, Goudie EB, Brooksbank AJ, Chesser TJS, Robinson CM. Smoking status and the disabilities of the arm shoulder and hand score are early predictors of symptomatic nonunion of displaced midshaft fractures of the clavicle. Bone Joint J 2016;98-B(Jan (1)):125–30.