

Clinical predictors of fracture in patients with shoulder dislocation: systematic review of diagnostic test accuracy studies

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ABSTRACT

Background Prereduction radiographs are conventionally used to exclude fracture before attempts to reduce a dislocated shoulder in the ED. However, this step increases cost, exposes patients to ionising radiation and may delay closed reduction. Some studies have suggested that prereduction imaging may be omitted for a subgroup of patients with shoulder dislocations.

Objectives To determine whether clinical predictors can identify patients who may safely undergo closed reduction of a dislocated shoulder without prereduction radiographs.

Methods A systematic review and meta-analysis of diagnostic test accuracy studies that have evaluated the ability of clinical features to identify concomitant fractures in patients with shoulder dislocation. The search was updated to 23 June 2022 and language limits were not applied. All fractures were included except for Hill-Sachs lesions. Quality assessment was undertaken using the Quality Assessment of Diagnostic Accuracy Studies 2 tool. Data were pooled and meta-analysed by fitting univariate random effects and multilevel mixed effects logistic regression models.

Results Eight studies reported data on 2087 shoulder dislocations and 343 concomitant fractures. The most important potential sources of bias were unclear blinding of those undertaking the clinical (6/8 studies) and radiographic (3/8 studies) assessment. The prevalence of concomitant fracture was 17.5%. The most accurate clinical predictors were age >40 (positive likelihood ratio (LR+) 1.8, 95% CI 1.5 to 2.1; negative likelihood ratio (LR-) 0.4, 95% CI 0.2 to 0.6), female sex (LR+ 2.0, 95% CI 1.6 to 2.4; LR- 0.7, 95% CI 0.6 to 0.8), first-time dislocation (LR+ 1.7, 95% CI 1.4 to 2.0; LR- 0.2, 95% CI 0.1 to 0.5) and presence of humeral ecchymosis (LR+ 3.0-5.7, LR- 0.8-1.1). The most important mechanisms of injury were high-energy mechanism fall (LR+ 2.0–9.8, LR- 0.4-0.8), fall >1 flight of stairs (LR+ 3.8, 95% CI 0.6 to 13.1; LR- 1.0, 95% CI 0.9 to 1.0) and motor vehicle collision (LR+ 2.3, 95% CI 0.5 to 4.0; LR- 0.9, 95% CI 0.9 to 1.0). The Quebec Rule had a sensitivity of 92.2% (95% CI 54.6% to 99.2%) and a specificity of 33.3% (95% CI 23.1% to 45.3%), but the Fresno-Quebec rule identified all clinically important fractures across two studies: sensitivity of 100% (95% CI 89% to 100%) in the derivation dataset and 100% (95% CI 90% to 100%) in the validation study. The specificity of the Fresno-Quebec rule ranged from 34% (95% CI 28% to 41%) in the derivation dataset to 24% (95% CI 16% to 33%) in the validation study.

WHAT IS ALREADY KNOWN ON THIS TOPIC

- ⇒ Shoulder dislocations are commonly associated with fractures of the proximal humerus, which may preclude closed reduction in the ED.
- ⇒ Plain radiographs are used to identify fractures but expose the patient to ionising radiation, delay definitive treatment and may inhibit appropriate prehospital attempts at reduction.

WHAT THIS STUDY ADDS

- ⇒ Clinical predictors can help risk stratify patients with a shoulder dislocation based on the likelihood of a concomitant clinically significant fracture.
- ⇒ Clinical prediction rules can help identify patients that could safely forgo radiography before closed reduction of a dislocated shoulder.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Clinical prediction rules can support shared decision making about early closed reduction of dislocated shoulders, particularly when there is an anticipated delay to imaging.

Conclusion Clinical prediction rules may have a role in supporting shared decision making after shoulder dislocation, particularly in the prehospital and remote environments when delay to imaging is anticipated.

BACKGROUND

Shoulder dislocation is a commonly encountered injury in the ED.¹ Isolated shoulder dislocations should undergo prompt closed reduction to alleviate pain, limit tension on soft tissue structures and restore anatomical alignment.² However, up to 25% of shoulder dislocations are associated with fracture of the proximal humerus.^{3–5} Concomitant fractures are important to identify as fracture of the humeral neck contraindicates closed reduction in the ED.6 Although tuberosity fractures are not an absolute contraindication,⁶⁷ they are important to identify as they increase the risk of iatrogenic humeral neck fracture during attempts at reduction.⁸ It is therefore conventional to obtain plain radiographs before attempting closed reduction of a clinically dislocated shoulder.² However, the need for plain



radiographs increases cost, delays reduction and exposes the patient to ionising radiation,^{9–11} which is a particular concern for young patients with recurrent dislocations. The perceived need for imaging might also inhibit prehospital attempts at closed reduction,¹² which may be particularly important in remote environments such as mountainous ski resorts.¹³

A number of studies have therefore tried to identify whether a there is a subgroup of patients for whom it is safe to omit prereduction radiographs despite a clinical diagnosis of shoulder dislocation.^{9 10}

This systematic review sought to determine whether clinical predictors can safely identify a subgroup of patients who might safely undergo closed reduction of a dislocated shoulder without prereduction radiographs.

METHODS

This systematic review was conducted according to the Preferred Reporting Items for Systematic Review and Meta-Analysis of Diagnostic Test Accuracy studies guidelines.¹⁴

Search strategy

Literature searches were designed with and performed by a specialist information librarian using PubMed, Ovid MEDLINE (from 1946 to November 2021), EBSCO CINAHL, Embase (from 1947 to 2021) and Web of Science. The search strategies are available in online supplemental file 1. The reference lists of included studies were screened for further items and a forward citation search undertaken for new studies using Google Scholar on 23 June 2022. Duplicates were removed using EndNote (Clarivate, Pennsylvania, USA) and unique items then imported into the specialist systematic review package Rayyan (Qatar Computing Research Institute, Doha, Qatar) for abstract screening.

Study selection

Studies were included if they reported the diagnostic characteristics of clinical findings (individually or in combination) for fracture in patients with a clinically dislocated shoulder. All glenohumeral joint dislocations (ie, anterior, posterior or inferior) were included. The reference standard was plain radiography, and a positive outcome was defined as the identification of a clinically significant fracture, which we defined pragmatically as any fracture with the exception of Hill-Sachs lesions. Studies were excluded if they did not include sufficient data to construct a 2×2 table. Two authors (IO and LC) independently screened abstracts and then full-texts with a third author (DM) available to arbitrate if necessary.

Data extraction and quality assessment

Data were extracted independently by two authors (IO and LC) and then compared for errors. Any inconsistencies were resolved through discussion with a third author (DM). If further data or clarification was required to construct 2×2 tables, the corresponding authors of included studies were contacted. Risk of bias was assessed using the Quality Assessment of Diagnostic Accuracy Studies 2 (QUADAS-2) tool.¹⁵ This assessment was performed independently by two authors (IO and LC) and then checked by a third (DM).

Statistical analysis

Sensitivity, specificity and likelihood ratios were calculated for each feature together with their 95% CIs. The unit of analysis was individual shoulders. Clinical predictors reported by

only one study were presented as individual data points and two studies as a range. Data about the same clinical predictor reported by three studies were pooled using univariate random effects models and data reported by four or more studies using multilevel mixed effects logistic regression models. Studies pooled using multilevel mixed effects logistic regression were also summarised using hierarchical summary receiver operating characteristic curve (HSROC) plots. Heterogeneity was evaluated using the I² test and by visualising HSROC plots before data were pooled. However, we anticipated significant heterogeneity and so planned to pool data using mixed effects models. Publication bias was assessed by visually inspecting scatter plots and by regressing the log diagnostic OR against 1/ESS1/22 weighted by ESS (where ESS represents the effective sample size) with p < 0.05 for the slope coefficient used as the threshold for significant asymmetry, as recommended by Deeks et al.¹⁶ Metaanalysis was undertaken using the diagti, midas, metan and metandi modules in Stata SE V.15. We planned to specifically highlight clinical features with a positive likelihood ratio (LR+) of >2.0 or a negative likelihood ratio (LR–) of <0.5.

RESULTS

There were 4688 unique items retrieved from the search process that included eight eligible^{3–5} ^{17–19} studies reporting data on 2087 individual shoulder dislocations and 343 concomitant fractures (figure 1). There was no evidence of publication bias.

Study and participant characteristics

The included studies are described in table 1. There were five retrospective³⁻⁵ ¹⁷ ²⁰ and three prospective studies¹⁸ ¹⁹ ²¹ from EDs in Australia,²⁰ Canada,⁴ ¹⁸ ¹⁹ France,¹⁷ Iran²¹ and Turkey.^{3 5} Three were published by a single research team⁴ ¹⁸ ¹⁹ but over non-overlapping time periods. Most studies included all adults aged >18^{4 5} ¹⁷⁻¹⁹ ²¹ or ≥16³, but one study limited its population to patients aged <40 years.²⁰

Risk of bias

Table 2 shows the risk of bias assessment for each study using the QUADAS-2 tool. Six studies were at low risk of bias in the patient selection category because they reported data from consecutive patients.^{4 5} 17-19 21 However, two studies were at high risk of patient selection bias.^{3 20} This is because one only included younger patients (aged <40 years), which may have distorted the diagnostic characteristics of predictors for fracture²⁰ and the other because only a minority (30%) of patients with a dislocated shoulder had complete medical records available.³ These issues also gave rise to the only applicability concerns across all of the QUADAS-2 domains. Six studies were at unclear risk of bias in the index test category because they were retrospective studies and did not explicitly state that the assessor recording clinical features was blinded to the results of the radiograph.^{4 5 17 18 20 21} Similarly, three studies were at unclear risk of bias in the reference standard category because they did not explicitly confirm that the assessor was blinded to the clinical features.^{4 20 21} All eight studies were judged to be at low risk of bias in the flow and timing category because a fracture was unlikely to have developed or resolved between clinical assessment and imaging.

Prevalence of concomitant fracture

Seven of the eight studies³⁻⁵ $^{17-19}$ ²¹ were used to estimate the prevalence of clinically significant fractures among the ED population with shoulder dislocations because Ong *et al* only included younger patients (aged <40).²⁰ There were therefore

Systematic review

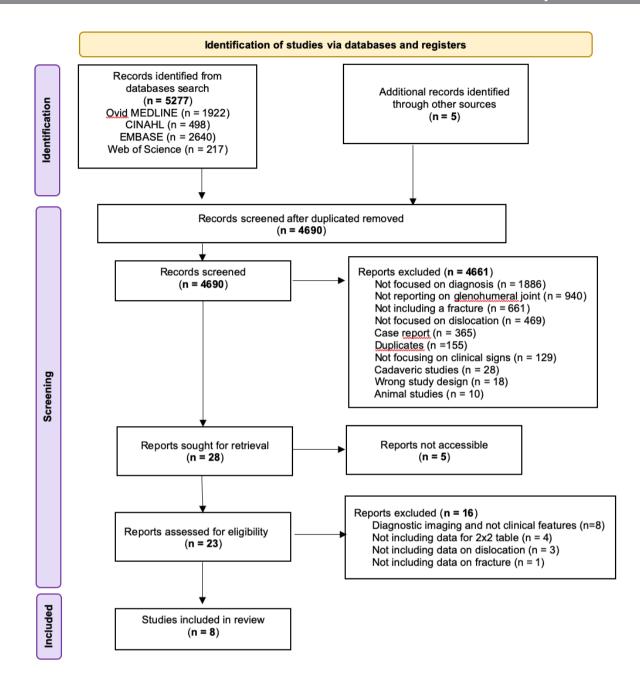


Figure 1 Preferred Reporting Items for Systematic Reviews and Meta-Analyses flow diagram showing inclusion of studies.

Table 1 Characteristics of studies included within the review						
Study	Design	Setting	Population	N	Clinically significant fractures (% of total)	
Emond <i>et al</i> ⁴	Retrospective case-control	Canada	All patients aged >18	334	85 (25.4)	
Emond <i>et al</i> ¹⁹	Prospective cohort	Canada	All patients aged >18	222	40 (18.0)	
Ong <i>et al</i> ²⁰	Retrospective case-control	Australia	All patients aged <40	196	12 (6.1)	
Émond <i>et al</i> ¹⁸	Prospective cohort	Canada	All patients aged >18	207	24 (11.6)	
Temiz and Das ⁵	Retrospective case-control	Turkey	All patients aged >18	248	63 (25.4)	
Bolvardi <i>et al</i> ²¹	Prospective cohort	Iran	All patients aged >18	143	4 (2.8)	
Durak and Atıcı ³	Retrospective case-control	Turkey	All patients aged >16	135	34 (25.2)	
Delattre Sousa <i>et al</i> ¹⁷	Retrospective case-control	France	All patients aged >18	602	81 (13.5)	

Table 2	Risk of bias assessments for included studies usin	a the Oualit	v Assessment of Diagnostic Accuracy	v Studies 2 tool

	Patient selection	t selection Index test			Reference standard		Flow and timing
Study	Risk of bias	Applicability	Risk of bias	Applicability	Risk of bias	Applicability	Risk of bias
Emond <i>et al</i> ⁴	+	+	?	-	?	-	+
Emond <i>et al</i> ¹⁹	+	+	+	-	+	-	+
Ong <i>et al</i> ²⁰	-	-	?	-	?	-	+
Émond <i>et al</i> ¹⁸	+	+	?	-	+	-	+
Temiz and Das ⁵	+	+	?	-	+	-	+
Bolvardi <i>et al</i> ²¹	+	+	?	-	?	-	+
Durak and Atıcı ³	-	-	+	-	+	-	+
Delattre Sousa <i>et al</i> ¹⁷	+	+	?	-	+	-	+

331 clinically significant fractures among the group of 1891 shoulder dislocations (prevalence 17.5%). Four studies described the prevalence of different fracture types. The most common fractures affected one or more tuberosities in isolation (121/183, 66.1%; four studies).^{3 4 18 19} The prevalence of fractures that would preclude closed reduction in the ED (eg, fractures of the humeral head or neck) was up to 15%. Other fractures included bony Bankart lesions (5/125, 4.0%; two studies)^{4 19} as well as isolated fractures of the glenoid and coracoid.

Accuracy of clinical assessment

The most useful clinical features were age >40 (LR+ 1.8, 95% CI 1.5 to 2.1; LR- 0.4, 95% CI 0.2 to 0.6; 1406 dislocations, four studies), female sex (LR+ 2.0, 95% CI 1.6 to 2.4; LR- 0.7, 95% CI 0.6 to 0.8; 1497 dislocations, five studies), first-time dislocation (LR+ 1.7, 95% CI 1.4 to 2.0; LR- 0.2, 95% CI 0.1 to 0.5; 1745 dislocations, six studies) and presence of humeral ecchymosis (LR+ 3.0-5.7, LR- 0.8-1.1; 426 dislocations, two studies). The most important mechanisms of injury were high-energy mechanism fall (LR+ 2.0-9.8, LR- 0.4-0.8; 381 dislocations, two studies), fall >1 flight of stairs (LR+ 3.8, 95% CI 0.6 to 13.1; LR- 1.0, 95% CI 0.9 to 1.0; 760 dislocations, three studies) and motor vehicle collision (LR+ 2.3, 95% CI 0.5 to 4.0; LR- 0.9, 95% CI 0.9 to 1.0; 1362 dislocations, four studies).

Five studies (1410 dislocations and 216 fractures) reported data on the accuracy of the Quebec rule, which mandates prereduction radiography for injuries satisfying any one of the following criteria: age >40 (one study used a threshold of >35 years³), first shoulder dislocation and high-risk mechanism.^{3 4 17 20 21} High-risk mechanisms were falling down more than one flight of stairs, fight/assault and motor vehicle collision.⁴ Four of the five studies reported overall favourable diagnostic characteristics of the Quebec rule, but a single study from Australia (limited to younger patients aged <40 years) was less encouraging.²⁰ This latter study reported a sensitivity of only 42% (95% CI 16% to 71%) and a specificity of 40% (95% CI 33% to 47%). When all five studies were pooled using a multilevel mixed effects logistic regression model, the Quebec rule had a sensitivity of 92.2% (95% CI 54.6% to 99.2%) and a specificity of 33.3% (95% CI 23.1% to 45.3%) (figure 2).

One study presented an algorithm (the Fresno-Quebec Rule (FQR)) to determine which patients with a clinically dislocated shoulder should undergo prereduction radiographs.¹⁸ The factors incorporated into this algorithm were atraumatic recurrent episode, age >35 and high-risk mechanism (figure 3). High-risk mechanisms in the FQR are defined as motor vehicle collision, assault, sports-related or fall of >10 ft. According to the derivation study (207 dislocations and 24 fractures), the

algorithm achieved a sensitivity of 100% (95% CI 89% to 100%) and a specificity of 34% (95% CI 28% to 41%) for identifying fractures (LR+ 1.9, 95% CI 1.6 to 2.3; LR- 0.1, 95% CI 0.0 to 0.6).¹⁸ This finding has been reproduced by a single retrospective study in Turkey (135 dislocations and 34 fractures), which also reported a sensitivity of 100% (95% CI 90% to 100%) and a specificity of 24% (95% CI 16% to 33%; LR+ 1.3, 95% CI 1.1 to 1.5; LR- 0.1, 95% CI 0.0 to 0.9).³

DISCUSSION

This systematic review suggests there is a subgroup of patients with shoulder dislocations for whom radiographs may be safely omitted before closed reduction. Identifying this group could reduce costs, exposure to ionising radiation and time to joint reduction.^{9 10}

All eight studies defined clinically significant fractures as including all fracture patterns except for Hill-Sachs lesions. However, the most common bony injury (isolated tuberosity fractures) does not preclude closed reduction in the ED,^{6 7} and so identifying this injury may not affect the immediate management. Nevertheless, there are a number of reasons why it might be helpful to identify this fracture before reduction. First, tuberosity fracture may herald an undisplaced fracture across the humeral neck and has been associated with iatrogenic humeral neck fracture during closed reduction.⁸ The identification of a tuberosity fracture should therefore lead to careful examination

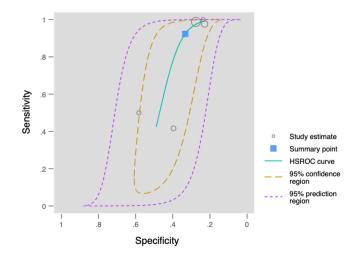
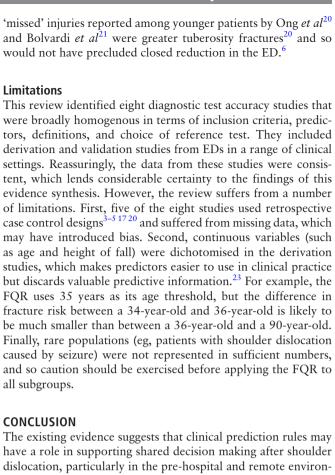


Figure 2 HSROC plot summarising accuracy of the Quebec rule for fracture. HSROC, hierarchical summary receiver operating characteristic curve.





have a role in supporting shared decision making after shoulder dislocation, particularly in the pre-hospital and remote environments when delay to imaging is anticipated. However, further external validation studies across different settings would be helpful.

Correction notice This article was resupplied on June 8th 2023 to include a CC-BY licence.

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Contributors IO led and undertook the initial systematic review. LC independently screened abstracts, extracted data and performed quality assessments. SG and AN contributed to the study design, data interpretation and critical review of the manuscript. DM designed and supervised the study then prepared the manuscript for publication and is the guarantor.

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Competing interests None declared.

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Patient consent for publication Not applicable.

Ethics approval Not applicable.

Provenance and peer review Not commissioned; externally peer reviewed.

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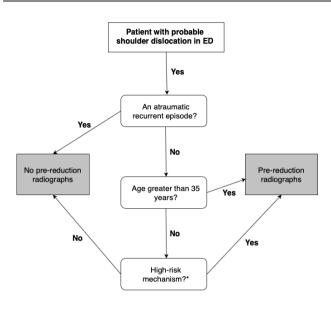


Figure 3 Fresno-Quebec rule reproduced from Émond et al.¹⁸

of the radiographs (ie, two orthogonal views) for evidence of an undisplaced fracture across the humeral neck.¹⁵ Second, tuberosity fractures may be difficult to appreciate on postreduction radiographs but often require orthopaedic follow-up and interval radiographs to exclude further displacement of the fragment.²² Finally, identification of a tuberosity fracture may reassure both the patient and emergency physician that this injury preceded attempts at closed reduction.

Studies across a range of settings have been consistent about the clinical features that are most useful for identifying patients with fractures. These features have been combined into a clinical decision rule-the Quebec rule-which recommends prereduction radiography in the case of a patient aged >40 years, a first episode of dislocation or a high-risk mechanism.⁴ The derivation study identified high-risk mechanisms as falling down more than one flight of stairs, fight/assault and motor vehicle collision.⁴ A number of validation papers supported this rule,^{3 4 17 20 21} but it performed much less well in a case-control study of younger patients from Australia.²⁰ In that study, the rule was only 42% sensitive for fracture. A subgroup analysis by Bolvardi et al similarly found that the rule was only 50% sensitive for fracture in patients aged <40 years.²¹ Although promising in some studies, the Quebec rule requires further validation in younger populations before it can be recommended for use in clinical practice.

The Fresno-Quebec Rule has been externally validated³ and maintained a sensitivity of 100% across two studies consisting of 342 shoulder dislocations and 58 clinically significant fractures.^{3 18 19} The rule is also supported by other diagnostic test accuracy studies that previously supported the accuracy of these features for identifying fractures.^{3 4 17 21} Nevertheless, although Ong et al did not evaluate the FQR directly, their data suggest the underlying predictors may not be sufficiently sensitive to safely exclude fracture among younger patients.²⁰ The FQR currently restricts its definition of 'high-risk mechanism' to falling from >10 ft, sports related, assault or motor vehicle collision.¹⁹ Only one of the four tuberosity fractures reported by Ong et al was atraumatic: two occurred after a fall from standing height and one during a seizure.²⁰ Clinicians should make their own judgement about the likelihood of fracture given each mechanism of injury and think more broadly than the specific high-risk mechanisms described by the FQR. However, reassuringly, all of the

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MEDLINE

Ovid MEDLINE(R) ALL <1946 to November 16, 2021>

- 1 physical examination.mp. or exp Physical Examination/ 1498784
- 2 physical exam*.mp. 105824
- 3 1 or 2 1507425
- 4 medical history taking.mp. or exp Medical History Taking/ 22463
- 5 3 or 4 1522319
- 6 "sensitivity and specificity".mp. or exp "Sensitivity and Specificity"/ 665185
- 7 "reproducibility of results".mp. or exp "Reproducibility of Results"/ 435570
- 8 observer variation.mp. or exp Observer Variation/ 44881
- 9 diagnostic test.mp. or exp Diagnostic Tests, Routine/ 32525
- 10 decision support techniques.mp. or exp Decision Support Techniques/ 81066
- 11 Humans/ or exp Decision Support Techniques/ 19919336
- 12 exp Bayes Theorem/ or bayes theorum.mp. 39945
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 20112445
- 14 shoulder dislocation.mp. or exp Shoulder Dislocation/ 6790
- 15 glenohumeral dislocation.mp. or exp Shoulder Dislocation/6262
- 16 glenohumeral joint dislocation.mp. 37
- 17 14 or 15 or 16 6855
- 18 fracture\$.mp. 330693
- 19 5 and 13 and 17 and 18 204

CINAHL

S1	(MH "Shoulder") OR "shoulder"	34,147
S2	(MH "Glenohumeral Joint") OR "glenohumeral joint"	10,209
S3	S1 OR S2	34,277
S4	(MH "Dislocations") OR "dislocations"	6,543
S5	(MH "Shoulder Dislocation") OR "shoulder dislocation or dislocated shoulder"	1,704
S6	"glenohumeral dislocation"	1,449
S7	(MH "Glenohumeral Joint") OR (MH "Dislocations") OR "Glenohumeral joint dislocation"	4,624
S8	S4 OR S5 OR S6 OR S7	8,761
S9	S3 AND S8	3,254
S10	(MH "Fractures+")	63,232
S11	(MH "Bone and Bones+")	139,875
S12	S10 OR S11	184,358
S13	S9 AND S12	979
S14	(MH "Diagnosis+") OR "diagnosis"	2,346,913
S15	(MH "Clinical Assessment Tools+") OR "clinical assessment tools AND clinical features"	264,342
S16	(MH "Signs and Symptoms+") OR "signs and symptoms"	720,667
S17	"clinical presentation"	14,023
S18	(MH "Physical Examination+") OR "physical examination+"	144,759
S19	(MH "Diagnostic Tests, Routine") OR "diagnostic test"	8,788
S20	(MH "Symptoms+")	8,878
S21	S14 OR S15 OR S16 OR S17 OR S18 OR S19 OR S20	2,693,874
S22	S13 AND S21	736

EMBASE

Embase Classic+Embase <1947 to 2021 Week 45>

- 1 Shoulder.mp. or exp shoulder/ or exp shoulder dislocation/ 153468
- 2 Glenohumeral joint.mp. or exp shoulder/ 88918
- 3 1 or 2 153543
- 4 exp dislocation/ or exp joint dislocation/ or Dislocation.mp. or exp fracture dislocation/ or exp shoulder dislocation/ 96981
- 5 Shoulder dislocation.mp. or exp shoulder dislocation/ 10281
- 6 Glenohumeral joint dislocation.mp. 41
- 7 Glenohumeral dislocation.mp. 320
- 8 4 or 5 or 6 or 7 96981
- 9 exp fracture/ or exp humeral supracondylar fracture/ or exp humerus fracture/ or Fracture.mp. or exp humeral head fracture/ or exp humerus shaft fracture/ or exp humeral neck fracture/ 443816
- 10 Fractures.mp. or exp fracture/ 400757
- 11 Humeral fracture.mp. or exp humerus fracture/ 14368
- 12 Bone fracture.mp. or exp fracture/ 357918
- 13 9 or 10 or 11 or 12 468889
- 14 3 and 8 and 135541
- 15 "Signs and symptoms".mp. or exp physical disease by body function/ 10605316
- 16 Clinical examination.mp. or exp clinical examination/ 150752
- 17 clinical feature/ or Clinical signs.mp. 823748
- 18 exp diagnosis/ or diagnostic features.mp. 7716162
- 19 15 or 16 or 17 or 18 15485733
- 20 "Sensitivity and specificity".mp. or exp "sensitivity and specificity"/ 444678
- 21 diagnostic accuracy.mp. or exp diagnostic accuracy/ 292613
- 22 sensitivity.mp. 1633565
- 23 Specificity.mp.989170
- 24 predictive.mp.621754
- 25 20 or 21 or 22 or 23 or 24 2652351
- 26 14 and 19 and 25 181

Web Of Science

#1) ((ALL=(Shoulder dislocation)) OR ALL=(glenohumeral dislocation)) ORALL=(glenohumeral joint dislocation)6,640

#2) (((ALL=(fracture)) OR ALL=(bone fracture)) OR ALL=(shoulder fracture)) OR ALL=(humeral fracture) <u>587,921</u>

#3) **(#1) AND #2** <u>1,942</u>

#4) (((((((ALL=(clinical features)) OR ALL=(physical examination)) OR ALL=(signs and symptoms)) OR ALL=(diagnostic factors)) OR ALL=(diagnostic features)) OR ALL=(diagnosis)) OR ALL=(signs)) OR ALL=(symptoms) 3,577,953

#5) (#3) AND (#4)

<u>469</u>