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Educational Objectives

After reading the article, participants should be able to discuss the diagnostic utility of the physical exam, ankle/brachial indices, and ultrasound in penetrating extremity trauma.

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CME Accuracy of Physical Examination, Ankle-Brachial Index, and Ultrasonography in the Diagnosis of Arterial Injury in Patients With Penetrating Extremity Trauma: A Systematic Review and Meta-analysis

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ABSTRACT

Background: Penetrating Extremity Trauma (PET) may result in arterial injury, a rare but limb- and life-threatening surgical emergency. Timely, accurate diagnosis is essential for potential intervention in order to prevent significant morbidity.

Objectives: Using a systematic review/meta-analytic approach, we determined the utility of physical examination, Ankle-Brachial Index (ABI), and Ultrasonography (US) in the diagnosis of arterial injury in emergency department (ED) patients who have sustained PET. We applied a test–treatment threshold model to determine which evaluations may obviate CT Angiography (CTA).

Methods: We searched PubMed, Embase, and Scopus from inception to November 2016 for studies of ED patients with PET. We included studies on adult and pediatric subjects. We defined the reference standard to include CTA, catheter angiography, or surgical exploration. When low-risk patients did not undergo the reference standard, trials must have specified that patients were observed for at least 24 hours. We used the Quality Assessment Tool for Diagnostic Accuracy Studies (QUADAS-2) to evaluate bias and applicability of the included studies. We calculated positive and negative likelihood ratios (LR+ and LR–) of physical examination ("hard signs" of vascular injury), US, and ABI. Using established CTA test characteristics (sensitivity = 96.2%, specificity = 99.2%) and applying the Pauker-Kassirer method, we developed a test–treatment threshold model (testing threshold = 0.14%, treatment threshold = 72.9%).

Results: We included eight studies (n = 2,161, arterial injury prevalence = 15.5%). Studies had variable quality with most at high risk for partial and double verification bias. Some studies investigated multiple index tests: physical examination (hard signs) in three studies (n = 1,170), ABI in five studies (n = 1,040), and US in four studies (n = 173). Due to high heterogeneity (I^2 > 75%) of the results, we could not calculate LR+ or LR– for hard

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signs or LR+ for ABI. The weighted prevalence of arterial injury for ABI was 14.3% and LR– was 0.59 (95% confidence interval [CI] = 0.48–0.71) resulting in a posttest probability of 9% for arterial injury. Ultrasonography had weighted prevalence of 18.9%, LR+ of 35.4 (95% CI = 8.3–151), and LR– of 0.24 (95% CI = 0.08–0.72); posttest probabilities for arterial injury were 89% and 5% after positive or negative US, respectively. The posttest probability of arterial injury with positive US (89%) exceeded the CTA treatment threshold (72.9%). The posttest probabilities of arterial injury with negative US (5%) and normal ABI (9%) exceeded the CTA testing threshold (0.14%). Normal examination (no hard or soft signs) with normal ABI in combination had LR– of 0.01 (95% CI = 0.0–0.10) resulting in an arterial injury posttest probability of 0%.

Conclusions: In PET patients, positive US may obviate CTA. In patients with a normal examination (no hard or soft signs) and a normal ABI, arterial injury can be ruled out. However, a normal ABI or negative US cannot independently exclude arterial injury. Due to high study heterogeneity, we cannot make recommendations when hard signs are present or absent or when ABI is abnormal. In these situations, one should use clinical judgment to determine the need for further observation, CTA or catheter angiography, or surgical exploration.

Penetrating Extremity Trauma (PET) is among the frequently encountered injuries in high-volume, urban trauma centers. Missiles from handguns inflict approximately 50% of these wounds with femoral and popliteal arteries being the most commonly injured.[1] While these injuries contribute to a relatively lower mortality due to exsanguination, morbidity may be substantial. In a review of the national trauma databank, Tan et al.[2] reported 3.8% mortality, 1.3% amputation, 11.9% fasciotomy, and 7.3% wound infection/venous thromboembolism rates among PET patients. Initial diagnosis and treatment of arterial injury and the overall management of PET has been the subject of debate, which is substantiated by the dissimilarity between the major evidence-based guidelines: The Eastern Association for the Surgery of Trauma (EAST) practice management guideline (2012)[3] and Western Trauma Association (WTA) position article, Parts I (2011)[4] and II (2013).[5] For example, the EAST and WTA do not completely agree on definitions of the "hard and soft signs" of vascular injury (Table 1) or the role of Ultrasonography (US). Adding to the uncertainty, some signs of vascular injury may be ambiguous in practice. "Proximity", a sign common to both guidelines,[3,4] requires that one judge an injury trajectory to have crossed the path of a major vessel *after* the injury has occurred. It is also generally accepted that injuries with hard signs should undergo immediate exploration in the operating room. Although routine imaging is not warranted in PET,[6] a wound without hard signs may still be harboring an arterial injury, and a systolic blood pressure index such as the Ankle-Brachial Index (ABI) may be used as an adjunct to physical examination to screen for such injury[7] (see Data Supplement S1 [available as supporting information in the online version of this paper, which is available at https://doi.org/onlinelibrary.wiley.com/doi/10.1111/acem.13227/full] for the technique used to obtain a systolic blood pressure index). The determination of hard or soft signs in the emergency department (ED) is crucial in the management of PET, both diagnostically with ABI and/or imaging and therapeutically with vascular intervention or operative repair. There is a paucity of published prospective, randomized clinical trials, and the study by Inaba et al.[8] demonstrating the equivalent diagnostic performance of CT Angiography (CTA) to catheter angiography remains the only level 1 data available. Several studies contribute to the formulation of the guidelines,[3,4] some of which describe the importance of physical examination[9,10] and ABI[7,11] and utility of imaging including US,[12] CTA,[8] and catheter angiography,[13,14] either individually or comparatively.[15] The guidelines[3,4] are based upon qualitative review of observational studies with expert consensus, and the void for a systematic and quantitative analysis of the available data is apparent. We developed an integrated approach to the diagnosis of arterial injury in patients following PET by utilizing a systematic review/meta-analytic approach. The primary aim of this review is to determine the diagnostic accuracy of physical

Table 1
Definition of Hard and Soft Signs by EAST and WTA Guidelines

Guideline	Hard Sign	Soft Sign
EAST	Expanding hematoma Bruit Thrill Pulse deficit Pulsatile bleeding	History of arterial bleeding Proximity of wound to artery Neurologic deficit Nonexpanding hematoma
WTA	Expanding hematoma Bruit Thrill Pulselessness Pallor Paresthesia Pain Paralysis External bleeding	History of arterial bleeding Proximity of wound to artery Neurologic deficit Small, nonpulsatile hematoma

EAST = Eastern Association for the Surgery of Trauma; WTA = Western Trauma Association.

examination, ABI, and US compared to the reference standard of CTA, catheter angiography, or surgical exploration in the diagnosis of arterial injury in patients presenting to the ED with PET.

METHODS

Study Design

We conducted a systematic review and meta-analysis of studies that examined the performance characteristics of the modalities used to evaluate penetrating trauma to the extremities. The systematic review was conducted using the Preferred Reporting Items for Systematic Review and Meta-analyses (PRISMA) guidelines.[16]

Search Strategy

The design and manuscript structure of this systematic review conform to the recommendations from the Meta-analysis of Observational Studies in Epidemiology (MOOSE) statement.[17] In conjunction with a medical librarian, eight investigators independently searched the medical literature in PubMed, Embase, and Scopus from inception to November 2016 for the search terms diagnosis and penetrating trauma. Diagnosis was searched under MeSH diagnosis, diagnosis-related groups, delayed diagnosis, computer-assisted diagnosis, early diagnosis, differential diagnosis, immunologic tests, US, or ankle brachial index. Penetrating extremity trauma was searched under MeSH penetrating, injuries, wounds and injuries, diagnosis, epidemiology, etiology, history, physiology, physiopathology, extremities, arm, or leg (Data Supplement S2, available as supporting information in the online version of this paper, which is available at https://doi.org/onlinelibrary.wiley.com/doi/10.1111/acem.13227/full). The PubMed, Embase, and SCOPUS searches were combined for the three separate search topics—physical examination, ABI, and US—and limited by human-subject and English-language articles. We also searched for abstracts at opengrey.eu, http://www.ntis.gov and clinicaltrials.gov and reviewed the scientific meetings of Society for Academic Emergency Medicine, American College of Emergency Physicians, and American College of Surgeons from 1996 to 2016. Studies were included if they recruited patients with PET who presented to the ED. All studies were cross-sectional, but for the purpose of this diagnostic review we defined "prospective" design as patient entry prior to receiving the index test. Narrative reviews, case reports, or studies focused on therapy were not included.

Types of Participants. We included studies that recruited adult and pediatric patients presenting to the ED with PET. Patients were not excluded based on comorbidities or concomitant traumatic injuries.

Types of Index Tests. We included studies that applied physical examination, ABI, and US as index tests for the diagnosis of arterial injury. The terminology to describe the systolic blood pressure indices varied among the trials (Doppler segmental pressure, arterial pressure index) and was also dependent on upper (brachial-brachial or wrist-brachial index) and lower-extremity testing (ABI). For simplification and consistency, we will use a common term, ABI, to represent all indices.

Types of Reference Standard. We included studies that used CTA, catheter angiography, or surgical exploration as a reference standard for the final diagnosis of arterial injury. In contemporary clinical practice, CTA has supplanted catheter angiography as the initial radiologic diagnostic assessment of penetrating extremity injuries. A systematic review and meta-analysis[18] has demonstrated the accuracy of CTA with 96.2% sensitivity and 99.2% specificity for arterial injury after penetrating trauma to the upper and lower extremity in both the adult and pediatric population. In trials where low-risk patients were not subjected to the reference standard, the methods must have specified that those patients underwent inpatient observation for at least 24 hours. It should be noted that our systematic review and meta-analysis did not examine the utility of CTA as a pre-procedural workup modality once the decision has been made to proceed to vascular intervention or surgery.

Data Abstraction. Two or more authors for each index test category independently selected articles from the combined PubMed/Embase/Scopus search for full-text review. Each reviewer independently selected potentially eligible studies before both authors agreed on the list of studies for full-text review. Any differences in study selection were resolved by consensus. Each author then applied the stated inclusion and exclusion criteria to determine which studies to include in our systematic review. Differences were resolved by consensus after discussion and adjudication. Two reviewers independently extracted the data from each of the included studies and reconstructed two-by-two tables. If data could not be gleaned from the body of the publications, we attempted to contact the investigators of those trials. When study data were unavailable for injured extremities, we performed the analysis on patients in that trial.

Data Analysis

Sensitivities, specificities, and likelihood ratios were calculated based on constructed two-by-two tables for each included study. To compute meta-analysis summary estimates when more than one study assessed the same index test, we combined test characteristic data using a random-effects model with MetaDiSc software.[19] Interstudy heterogeneity was assessed for pooled estimates of sensitivity and specificity using the DerSimonian-Laird random-effects model.[20] We pooled data only when I^2 was less than 75% and report point estimates for variables that showed high heterogeneity.[21] When I^2 was greater than 75%, we studied the potential sources of heterogeneity. We investigated differences in patient demographics, study setting, and overall quality and risk of bias based upon the results of QUADAS-2. Sensitivity analysis was conducted after removal of possible outliers. We applied Bayes' theorem using the weighted prevalence of arterial injury in each index test group as the pretest probability and the pooled positive and negative likelihood ratios (LR+ and LR–) for each index test to estimate the positive and negative posttest probabilities of arterial injury. Publication bias was not assessed because of the questionable validity of this approach in diagnostic meta-analyses.[22]

Individual Trial Quality Appraisal

For each index test group (physical examination, ABI, and US) two authors used the Quality Assessment Tool for Diagnostic Accuracy Studies (QUADAS-2)[23] for systematic reviews to evaluate risk of bias and applicability of included trials. Four domains were assessed for risk of biases: 1) patient selection, 2) index test, 3) reference test, and 4) flow and timing. In addition, the tool enables authors to rate how well each study's 1) patient selection, 2) index test, and 3) reference standard apply to the specific research question posed by the systematic review. For the purposes of this diagnostic systematic review, several considerations were established a priori to assess the quality of individual trials, and a set of "yes" or "no" signaling questions were developed for each domain of QUADAS-2.

The ideal patient population would be patients who presented to an ED with PET and subsequently received both index test and reference test with the interpreter of each test blinded to the results of the other. Given that multiple index tests were reviewed across included studies, we decided to judge the appropriateness of inclusion/exclusion criteria based on the individual index test. For physical examination studies, an exclusion based on severity of the injury or presence/absence of signs was judged to be inappropriate. Conversely, for ABI or US, the exclusion of patients who were transferred directly to the operating room due to severity of injury was considered appropriate. Typically, ABI and US are used to assist with the management of less severe cases who do not have hard signs of vascular injury.

If the point of index test execution time was not clearly specified or the index test was performed after acknowledgment of the result of the reference test, then that domain of QUADAS-2 would be at high risk for bias. For ABI and US, the criteria for a positive test needed to be clearly defined for that study to be at low risk of bias. For physical examination, the decision to qualify a finding as positive or negative was left to physician discretion. We judged the index-reference test interval to be appropriate if patients received the index test upon presentation to the ED and were then promptly sent for CTA, catheter angiography, or surgical exploration. If the point of execution of the reference test was not clearly specified or the interpreter of the reference test was cognizant of the result of the index test, then that domain of QUADAS-2 would be at risk of bias. Concerns regarding the applicability of the results of index or reference testing were raised if these tests were conducted in a manner that differed from routine clinical practice. For example, if advanced US or CTA technology were used only for the trial but not routinely available in practice, then the corresponding domain of QUADAS-2 would be judged as "low applicability."

An unweighted Cohen's Kappa was calculated to measure agreement. Statistical agreement between the reviewers was assessed via a kappa analysis using SPSS (Version 20, IBM Corp.NY). Two of the authors individually rated the QUADAS-2 assessment for each index test.

Test–Treatment Threshold

The Pauker and Kassirer[24] decision threshold model was used to determine testing and treatment thresholds. This model is based on the consideration of five variables: sensitivity, specificity, risk of a diagnostic test, risk of treatment (Rrx), and anticipated benefit of treatment (Brx). Estimates of these variables were abstracted from the literature to derive theoretical testing and treatment thresholds in patients with PET.

RESULTS

The PubMed, Embase, and Scopus searches identified 162 citations for examination, 1,078 citations for ABI, and 78 citations for US. Upon review of the bibliography of the reviewed articles, six more citations were found. Eight studies[8,25–31] were included in our review (Figure 1). Tables 2–4 describe the included studies, and some studies[8,25–28] investigated multiple index tests. The combined sample size was 2,161 of which 335 had arterial injury. Prevalence of arterial injury ranged from 5%[28] to 41%[31] with weighted prevalence of 15.5% (95% confidence interval [CI] = 14.0%–17.0%).

QUADAS-2 Analysis of Included Studies

Initial inter-rater reliability between the two QUADAS reviewers was substantial (κ = 0.62, 95% CI = 0.51–0.71). All disagreements were resolved by consensus, and all authors agreed 100% on the final QUADAS-2 scoring (Figure 2).

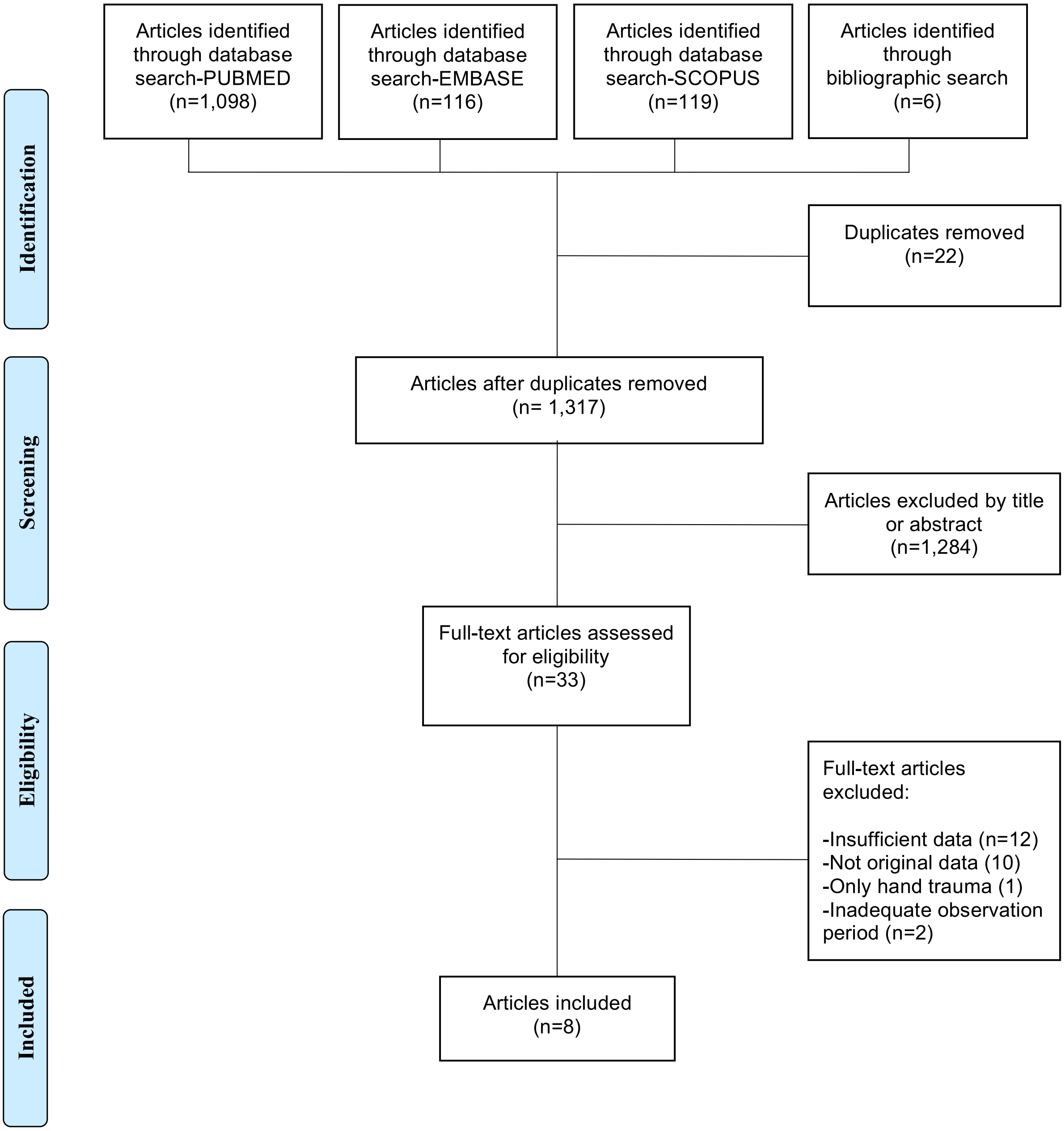

Figure 1. Study selection process.

Table 2
Description of Included Studies for Physical Examination

Study	Design	Subject Characteristics	Reference Standard or Observation Period and Follow-up	Hard and Soft Sign Definitions	Trial Arterial Injury Prevalence, % (95% CI)
Schwartz et al., 1993[25]	Prospective	Inclusion: • Unilateral, isolated, PET Exclusion: • Bilateral injuries Sample size: 469 patients/extremities Median age: 27 y Age range: 14–68 y Sex: 91% male Most frequent mechanism: gunshot (73%)	Reference standard: • Catheter angiography Observation period: • Inpatient observation for 24 h Follow-up: • 1–8 wk	Hard signs: • Shotgun injury • Pulse deficit • Neurologic deficit Soft signs: • History of hemorrhage or hypotension • Hematoma • Bruit • Fracture • Major soft tissue defect • Delayed capillary refill	16.4 (13.3–20.1)
Gonzalez and Falimirski, 1999[26]	Prospective	Inclusion: • PET • Proximity to major artery Exclusion: Not reported Sample size: 406 patients/489 extremities Mean age: 25.3 y Age range: 6–72 y Sex: 88% male Most frequent mechanism: gunshot (83%)	Reference standard: • Operative findings • Catheter angiography Observation period: • Inpatient observation for 24 h Follow-up: • Not reported	Hard signs: • Active hemorrhage • Expanding or pulsatile hematoma • Pulse deficit • Bruit • Thrill Soft signs: • History of hemorrhage • Hypotension • Deficit of anatomically related nerve • Stable, nonpulsatile hematoma	10.2 (7.8–13.2)
Inaba et al., 2011[8]	Prospective	Inclusion: • Age 16 y or older • PET • Crush/blunt mechanism with long bone fracture or dislocation Exclusion: • Emergent cavitary surgery Sample size: 635 patients (212 penetrating trauma) Mean age: not reported Age range: not reported Sex: not reported Most frequent mechanism: not reported	Reference standard: • Operative findings • CTA Observation period: • Inpatient observation $\geq$ 24 h Follow-up: • 3.1 $\pm$ 1.7 d (mean)	Hard signs: • Active hemorrhage • Expanding or pulsatile hematoma • Pulse deficit • Bruit • Thrill • Limb Ischemia • Compartment syndrome • Shock Soft signs: • Venous oozing • Nonexpanding or nonpulsatile hematoma • Diminished distal pulses	16.0 (11.7–21.6)

CTA = CT angiography; PET = penetrating extremity trauma.

Table 3
Description of Included Studies for Ankle-Brachial Index

Study	Design	Subject Characteristics	Device/Operator	Index Test Threshold	Reference Standard or Observation Period and Follow-up	Trial Arterial Injury Prevalence, % (95% CI)
Anderson et al., 1990[27]	Prospective	Inclusion: • PET Exclusion: Not reported Sample size: 454 patients/514 extremities (23 ABI) Mean age: 27 y Age range: 5–65 y Sex: 95.4% male Most frequent mechanism: gunshot (88.3%)	Device: • Doppler Flowmeter (Model 811, Parks) Operator: • Not reported	Segmental or contralateral difference of ≥ 0.15	Catheter angiography	26.1 (12.3–46.8)
Schwartz et al., 1993[25]	Prospective	Inclusion: • Unilateral, isolated, PET Exclusion: • Bilateral injuries Sample size: 469 patients/extremities Median age: 27 y Age range: 14–68 y Sex: 91% male Most frequent mechanism: gunshot (73%)	Device: • 5-MHz hand-held Doppler probe Operator: • Admitting surgeon	0.9	Reference standard: • Catheter angiography Observation period: • Inpatient observation for 24 h Follow-up: • 1–8 wk	16.4 (13.3–20.1)
Gagne et al., 1995[28]	Prospective	Inclusion: • Penetrating lower-extremity injury • Proximity to major vascular bundle Exclusion: • Limb ischemia • Diminished or absent pulses • Large or expanding hematoma • Hemorrhage with hypotension • Bruit/thrill • Anatomically related neurologic deficit Sample size: 37 patients/40 extremities (25 ABI) Mean age: 24.6 y Age range: 14–42 y Sex: 94.6% male Most frequent mechanism: gunshot (100%)	Device: • Hand-held Doppler • Ultrasonic-flow detector Operator: • Vascular technologist • Surgical chief resident	0.9	Reference standard: • Catheter angiography Observation period: • Not reported Follow-up: • 11.75 mo (range 1 wk–18.25 mo)	5.0 (0.5–17.4)

(Continued)

Table 3 (continued)

Study	Design	Subject Characteristics	Device/Operator	Index Test Threshold	Reference Standard or Observation Period and Follow-up	Trial Arterial Injury Prevalence, % (95% CI)
Nassoura et al., 1996[29]	Prospective	Inclusion: • PET • Proximity to major artery Exclusion: • Soft or hard signs • Blunt trauma • Shotgun injury • Refusal of angiography • Allergy to contrast media Sample size: 298 patients/323 extremities Mean age: 27.3 y Age range: 9–65 y Sex: 92.6% male Most frequent mechanism: not reported	Device: • Unspecified Doppler Operator: • Not reported	0.9	Catheter angiography	12.4 (9.2–16.5)
Inaba et al., 2011[8]	Prospective	Inclusion: • Age 16 y or older • PET (gunshot, shotgun, or stab wound) • Crush injury to extremities or any other blunt mechanism resulting in long-bone fracture or dislocation Exclusion: • Emergent cavitary surgery Sample size: 635 patients (200 ABI) Mean age: not reported Age range: not reported Sex: not reported Most frequent mechanism: not reported	Device: • Not reported Operator: • Attending surgeon	0.9	Reference standard: • Operative findings • CTA Observation period: • Inpatient observation for ≥ 24 h Follow-up: • 3.1 ± 1.7 d (mean)	8.0 (4.9–12.7)

ABI = extremities or patients studied with ankle-brachial, brachial-brachial, or wrist-brachial index; CTA = CT angiography; PET = penetrating extremity trauma.

Table 4
Description of Included Studies for Ultrasonography

Study	Design	Subject Characteristics	Device/Operator	Reference Standard	Trial Arterial Injury Prevalence, % (95% CI)
Anderson et al., 1990[27]	Prospective	Inclusion: • PET Exclusion: not reported Sample size: • 454 patients/514 extremities (23 US) Mean age: 27 y Age range: 5–65 y Sex: 95.4% male Most frequent mechanism: gunshot (88.3%)	Device: • BioSound 2000 Image acquisition: • Radiologist Image interpretation: • Radiologist	Catheter angiography	26.1 (12.3–46.8)
Bergstein et al., 1992[30]	Prospective	Inclusion: • PET • No diminished pulses • No neurologic deficit • Nonexpanding hematoma • History of hemorrhage controlled at initial assessment Exclusion: • Ongoing hemorrhage • Obvious limb ischemia • Vessel occlusion • Expanding hematoma Sample size: 67 patients/75 extremities Median age: Not reported Age range: Not reported Sex: Not reported Most frequent mechanism: gunshot (84%)	Device: • ATL Ultramark (Advanced Tecnhology Laboratories) Image acquisition: • Registered vascular technologist • Vascular surgical fellow Image interpretation: • Registered vascular technologist • Vascular surgical fellow	Catheter angiography	5.3 (1.7–13.3)
Gagne et al., 1995[28]	Prospective	Inclusion: • Penetrating lower-extremity trauma • Proximity to major vascular bundle Exclusion: • Limb ischemia • Diminished or absent pulses • Large or expanding hematoma • Hemorrhage with hypotension • Bruit • Thrill • Anatomically related neurologic deficit Sample size: 37 patients/40 extremities (36 US) Median age: 24.6 y Range: 15–42 y Sex: 95% male Most frequent mechanism: gunshot (100%)	Device: • ACUSON XP5 or 128 Image acquisition: • Registered vascular technologist Image interpretation: • Not reported	Catheter angiography	5.0 (0.5–17.4)
Kuzniec et al., 1998[31]	Prospective	Inclusion: • Penetrating neck/extremity trauma Exclusion: • No hard signs • Hemodynamic fluctuation Sample size: 47 patients/51 extremities (39 US) Median age: 26.5 y Age range: 2–53 y Sex: 91.5% male Most frequent mechanism: gunshot (94.1%)	Devices: • Phillips Quantum 1000 • Toshiba 140 • Aloka 650 Image acquisition: • Registered vascular technologist Image interpretation: • Not reported	Catheter angiography	41.0 (27.0–57.6)

PET = penetrating extremity trauma; US = extremities studied with ultrasonography.

Patient Selection. We found one study for physical examination (Schwartz et al.[25]) to be at high risk of spectrum bias. Schwartz et al.[25] excluded all patients with bilateral injuries, which can result in the exclusion of more severe cases and consequently decrease the arterial injury prevalence. We found two studies for

ABI (Gagne et al.[28] and Nassoura et al.[29]) and one study for US (Gagne et al.[28]) to be at high risk of spectrum bias. In comparison to all other studies that did not limit inclusion by anatomical location of injury, Gagne et al.[28] and Nassoura et al.[29] included only injuries in proximity to major vessels and excluded all patients with hard or any other soft signs of vascular injury. The analysis of patients with only proximity wounds would have the effect of inflating arterial injury prevalence; the exclusion of patients with hard or any other soft signs of vascular injury would deflate arterial injury prevalence. Although these biases may have opposing and perhaps even negligible effects on baseline prevalence, their effects on the performance characteristics of ABI are unpredictable. The studies on physical examination[8,25,26] are at a high risk of partial verification bias. Partial verification bias occurs when patients with a positive index test are more likely to undergo the reference test.[32] Thus, to avoid partial verification bias, application of the reference test should not be determined by the result of the index test. In studies that examine the accuracy of physical examination,[8,25,26] patients with signs of vascular injury were more likely to undergo CTA, catheter angiography, or surgical exploration. The use of 24-hour inpatient observation for those without signs of vascular injury can, to some degree, reduce the risk of partial verification bias in these studies.[8,25,26]

Index Test. The interpreter of the index test (physical examination, ABI, US) was blinded to the reference test (CTA, catheter angiography, or intraoperative findings) in all studies. With the exception of Anderson et al.[27] and Gagne et al.[28] for US, the threshold or criteria for positive test was prespecified for both ABI and US in all studies. Anderson et al.[27] used B-mode US for the detection of arterial injury as compared to Gagne et al.,[28] Bergstein et al.,[30] and Kuzniec et al.[31] who employed color-flow duplex US. Therefore, we assessed the results from Anderson et al.[27] to have “low applicability.”

Reference Test. Several studies[8,25–29] failed to specify blinding of the interpreter of the reference test to the results of the index test. This can introduce incorporation bias; that is, the result of the index test may influence whether the reference test classifies a patient as disease-positive or disease-negative. Incorporation bias may falsely elevate the calculated sensitivity and specificity and consequently increase the observed LR+ and decrease the observed LR–.

Flow and Timing. We found three studies (Inaba et al.,[8] Schwartz et al.,[25] and Gonzalez and Falimirski[26]) to be at high risk of differential verification bias. Differential verification bias, as described by Kohn et al.,[32] may occur when patients with a positive index test are more likely to undergo an immediate reference test, whereas those with negative index test are only followed clinically. These three trials[8,25,26] used inpatient observation for at least 24 hours and then outpatient follow-up as a surrogate for the reference

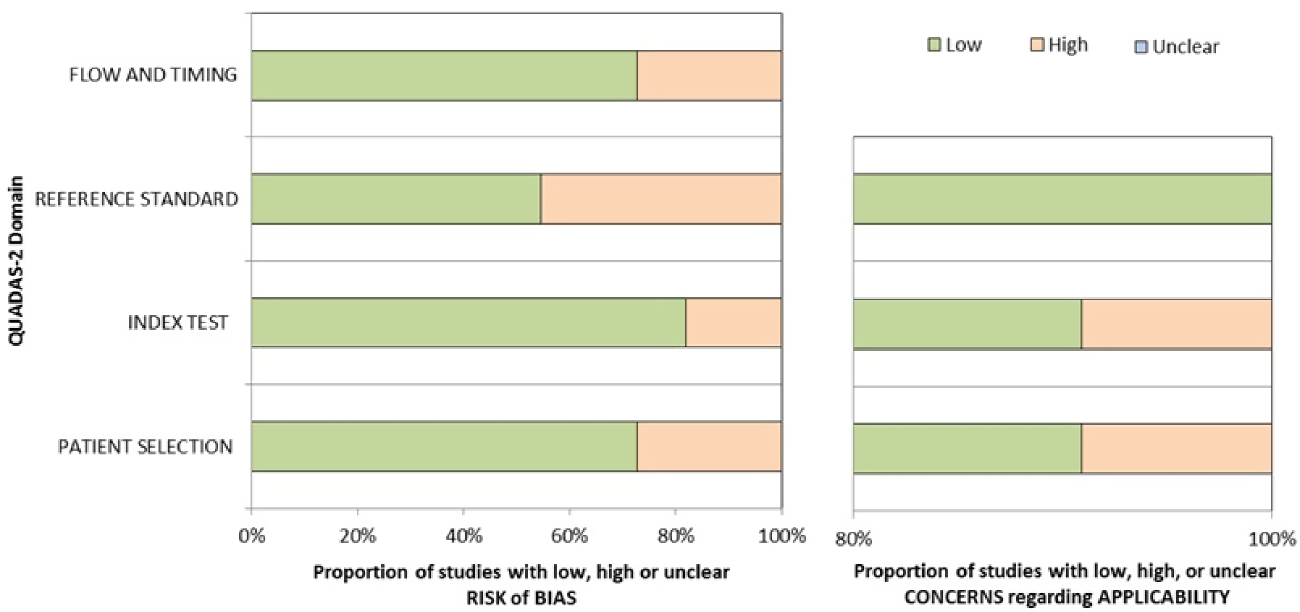

Figure 2. QUADAS-2 assessment of included studies for bias and applicability.

standard in patients with wounds that were judged to be low-risk for arterial injury. However, observation is not a perfect replacement for the reference standard, as less severe injuries may be missed and then resolve without intervention. This may result in a decrease in "false negatives" and an increase in "true negatives," which will then falsely increase both sensitivity and specificity of the index test.

Physical Examination

Three studies[8,25,26] (*n* = 1,170) provided the data for physical examination (Table 2). The prevalence of arterial injury in the trials ranged from 10.2%[26] to 16.4%[25] with weighted prevalence of 13.8% (95% CI = 11.9%–15.9%; Table 5). All reviewed studies were prospective in design. However, the inclusion criteria were not uniform across studies. While Inaba et al.[8] included all patients with PET, Schwartz et al.[25] limited their study population to those with isolated, unilateral injuries, and Gonzalez and Falimirski[26] only included patients whose wound trajectories were judged to traverse the path of a major vessel (proximity injury). Sample sizes ranged from 212[8] to 489.[26] Inaba et al.[8] did not provide demographic data of the participants. The mean[26] and median[25] ages of patients were similar in the remaining two studies (25.3[26] and 27[25] years), and the majority of patients were male (88%[26] and 91%[25]). Schwartz et al.[25] and Gonzalez and Falimirski[26] reported the most common mechanism of injury (gunshot, 73%[25] and 83%[26]). All three trials[8,25,26] observed patients who did not receive the reference test for at least 24 hours and attempted outpatient follow-up. However, the studies either lost patients to follow-up[25] or do not provide data on the outcome of the follow-up.[8,26] None of the trials reported intra- or inter-rater reliability of physical examination findings.

Performance Characteristics of Physical Examination

The finding of hard signs of vascular injury was too heterogeneous ($I^2 > 75\%$), which precluded pooled test characteristics, so we report only the point estimates. Presence of hard signs demonstrated LR+ from 2.89[25] to 210[8] ($I^2 = 96.5\%$), and absence of hard signs provided LR– from 0.08[26] to 0.61[25] ($I^2 = 92.6\%$; Table 5, Figure 3). The high heterogeneity can be attributed to varying definitions of hard and soft signs of vascular injury amidst the trials (Table 2). There was some overlap of hard and soft signs among the studies as well. Specifically, a neurologic deficit was considered a hard sign in Schwartz et al.[25] but a soft sign in Gonzalez and Falimirski.[26] Bruit was classified as a hard sign in Gonzalez and Falimirski[26] and Inaba et al.[8] but a soft sign in Schwartz et al.[25] We attempted to contact the authors to further divide participants into subgroups based upon individual hard or soft signs but were unable to obtain these data.

Ankle-Brachial Index

Five studies[8,25–29] (*n* = 1,040) produced the data for ABI (Table 3). The prevalence of arterial injury in the trials ranged from 5.0%[28] to 26.1%[27] with weighted prevalence of 14.3% (95% CI = 11.9%–17.1%; Table 6). All the reviewed studies were prospective in design and used PET as an inclusion criterion. The inclusion criteria in Schwartz et al.[25] were further limited and have been described previously. Gagne et al.[28] included only patients with lower-extremity gunshot wounds in proximity to a major vascular bundle and no hard or other soft signs. Sample sizes varied from 23[27] to 469[25] across the studies. Inaba et al.[8] did not provide demographic information for all patients. The mean[27–29] and median[25] patient ages

Table 5
Performance Characteristics of Physical Examination Hard Signs

Study	N	Arterial Injury Prevalence, % (95% CI)	Sensitivity, % (95% CI)	Specificity, % (95% CI)	LR+ (95% CI)	LR– (95% CI)
Schwartz et al., 1993[25]	469	16.4 (13.3–20.1)	49.4 (38.0–61.0)	82.9 (79.0–86.0)	2.89 (2.11–3.95)	0.61 (0.49–0.76)
Gonzalez and Falimirski, 1999[26]	489	10.2 (7.8–13.2)	92.2 (81.0–98.0)	95.2 (93.0–97.0)	19.2 (12.56–29.4)	0.08 (0.03–0.21)
Inaba et al., 2011[8]	212	16.0 (11.7–21.6)	58.8 (41.0–75.0)	100 (98.0–100)	210 (13.0–3,386)	0.41 (0.28–0.61)
Pooled	**1,170**	**13.8 (11.9–15.9)**	**[I^2 = 93.2%]**	**[I^2 = 97.0%]**	**[I^2 = 96.5%]**	**[I^2 = 92.6%]**

Pooled data are reported when $I^2 \leq 75\%$.
LR = likelihood ratio.

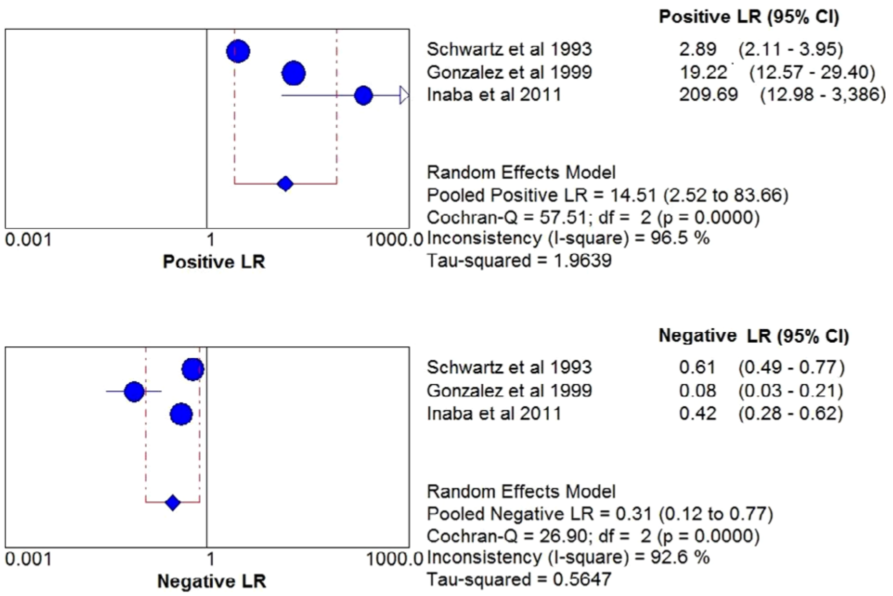

Figure 3. Forest plots for physical examination hard signs. LR = likelihood ratio.

were similar among the four other studies (24.6[28]–27.3 years[29]), and male sex predominated (91%[25]–95.4%[27]). The most common mechanism of penetrating injury (gunshot) was reported in three trials[25,27,28] and ranged from 73%[25] to 100%.[28] Anderson et al.[27] and Gagne et al.[28] studied a convenience sample of extremities for which ABI was measured prior to the reference test of catheter angiography. Inaba et al.,[8] Schwartz et al.,[25] and Nassoura et al.[29] studied all patients with ABI who did not have hard signs of vascular injury, and ABI was also measured prior to the reference standard. All trials except Inaba et al.[8] specified the use of Doppler-derived measurements, but only Schwartz et al.[25] and Nassoura et al.[29] explicitly defined the technique to obtain those measurements. Anderson et al.,[27] Schwartz et al.,[25] and Gagne et al.[28] described the Doppler device. Three trials (Inaba et al.,[8] Schwartz et al.,[25] and Gagne et al.[28]) reported the clinician who measured the ABI. In comparison to the other studies that used an index cutoff of 0.9, Anderson et al.[27] considered the ABI abnormal when the segmental or contralateral limb difference in the calculated lower-extremity segment to arm pressure index was greater than or equal to 0.15. Schwartz et al.[25] studied various ABI ranges (≥1.00, <1.00, <0.95, and <0.9). We separated the data from Schwartz et al.[25] using the index cutoff 0.9 and considered indices less than 0.9 to be abnormal. Inaba et al.[8] and Schwartz et al.[25] attempted outpatient follow-up for patients who did not undergo the reference test. The follow-up ranged from 3.1 ± 1.7 days[8] to 18.25 months,[28] and attrition was high (63%[25]) when reported. Inaba et al.[8] did not provide data on the outcome of their follow-up. None of the trials reported intra- or inter-rater reliability of ABI measurements.

Table 6
Performance Characteristics of Ankle-Brachial Index

Study	N	Arterial Injury Prevalence, %* (95% CI)	Sensitivity, % (95% CI)	Specificity, % (95% CI)	LR+ (95% CI)	LR– (95% CI)
Anderson et al., 1990[27]	23	26.1 (12.3–46.8)	66.7 (22.3–95.7)	100 (80.5–100)	23.1 (1.42–376)	0.37 (0.14–1.00)
Schwartz et al., 1993[25]	469	16.4 (13.3–20.1)	46.8 (35.3–58.5)	84.9 (81.0–88.3)	3.11 (2.22–4.34)	0.63 (0.51–0.78)
Inaba et al., 2011[8]	200	8.0 (4.9–12.7)	56.3 (29.9–80.2)	95.1 (90.9–97.7)	11.5 (5.33–24.8)	0.46 (0.26–0.80)
Pooled	**692**	**14.3 (11.9–17.1)**	**49.5 (39.3–60.1)**	**[I^2 = 89.2%]**	**[I^2 = 81.7%]**	**0.59 (0.49–0.72)**

Pooled data are reported when $I^2 \leq 75\%$.
LR = likelihood ratio.

Performance Characteristics of ABI

Upon analysis of the studies in the ABI group, we established Nassoura et al.[29] as a statistical outlier. Nassoura et al.[29] had a LR+ of 409 compared to the other studies in the group (3.1[25]–23[27]). Nassoura et al.[29] included only extremities with proximity injuries and without other signs of vascular injury, and therefore we excluded the trial from meta-analysis. We also excluded Gagne et al.[28] from meta-analysis. Similar to Nassoura et al.,[29] Gagne et al.[28] also included only patients with proximity injuries and without other signs. Gagne et al.[28] studied 25 extremities with ABI and did not report any positive results. Without any positive test results, it is impossible to analyze the data and report the performance characteristics for ABI from this trial.[28] Heterogeneity of the remaining included studies[8,25,27] was still too high to pool LR+ for abnormal ABI (LR+ = 3.11[25]–23.1,[27] I^2 = 81.7%); however, we calculated a pooled LR– of 0.59 (95% CI = 0.49 to 0.72, I^2 = 0%) for normal ABI (Table 6, Figure 4). Applying Bayes' theorem, using the weighted prevalence in the ABI group (14.3%) as an estimate of pretest probability and LR– 0.59 would result in a reduction of arterial injury posttest probability from 14.3 to 9% (95% CI = 8%–10%; Figure 5).

Performance Characteristics of Physical Examination With ABI

Appreciating the variable definition of hard and soft signs among the physical examination trials (Table 2) and the high trial heterogeneity within both physical examination and ABI groups, we sought the performance characteristics of "no hard or soft signs" in conjunction with a normal ABI. We found two studies (Inaba et al.[8] and Schwartz et al.[25]) that had matching samples with these attributes. After pooling the data from these two studies,[8,25] we found the combination of physical examination and ABI to be exceptional at ruling out arterial injury. A normal physical examination without hard or soft signs (as defined by each of the trials[8,25]) with normal ABI resulted in LR– 0.01 (95% CI = 0.0–0.1, I^2 = 0%; Table 7, Figure 6). Applying Bayes' theorem, using the weighted prevalence in the physical examination plus ABI subgroup (16.3%) as an estimate of pretest probability and LR– 0.01, the posttest probability of an arterial injury would be reduced from 16.3% to 0% (95% CI = 0%–1%; Figure 5).

Ultrasonography

Four studies[27,28,30,31] (*n* = 173) provided the data for US (Table 4). The prevalence of arterial injury in the trials ranged from 5.0%[28] to 41%[31] with weighted prevalence of 18.9% (95% CI = 13.3%–26.4%; Table 8). All the studies were prospective in design and used PET as an inclusion criterion. In all studies, the presence of hard signs was an exclusion criterion. Sample sizes varied from 23[27] to 75[30] extremities. The mean (27 years[27]) and median ages (24.6[28] and 26.5 years[31]) were similar, and male sex predominated in all studies (91.5[31]–95.4%[27]). Anderson et al.,[27] Gagne

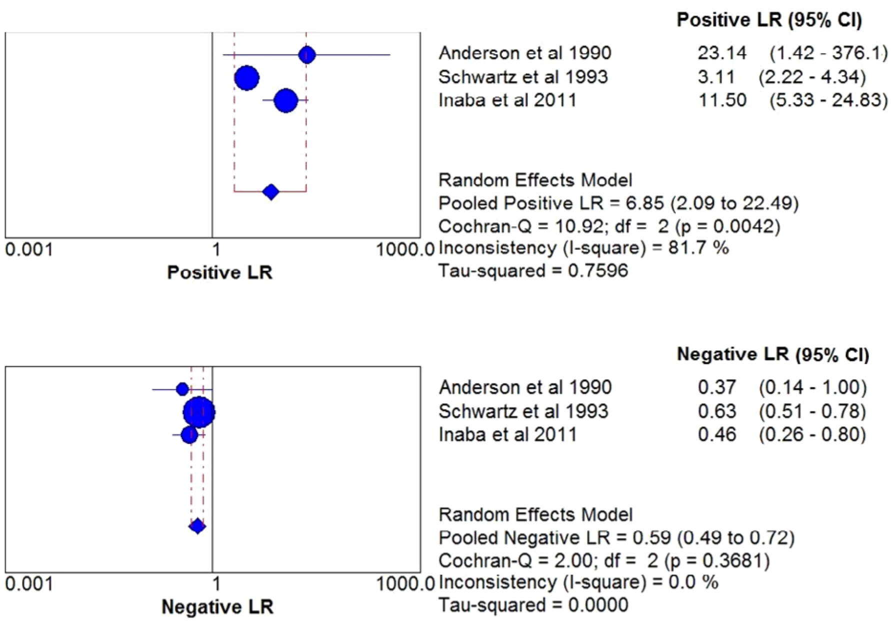

Figure 4. Forest plots for ankle-brachial index. LR = likelihood ratio.

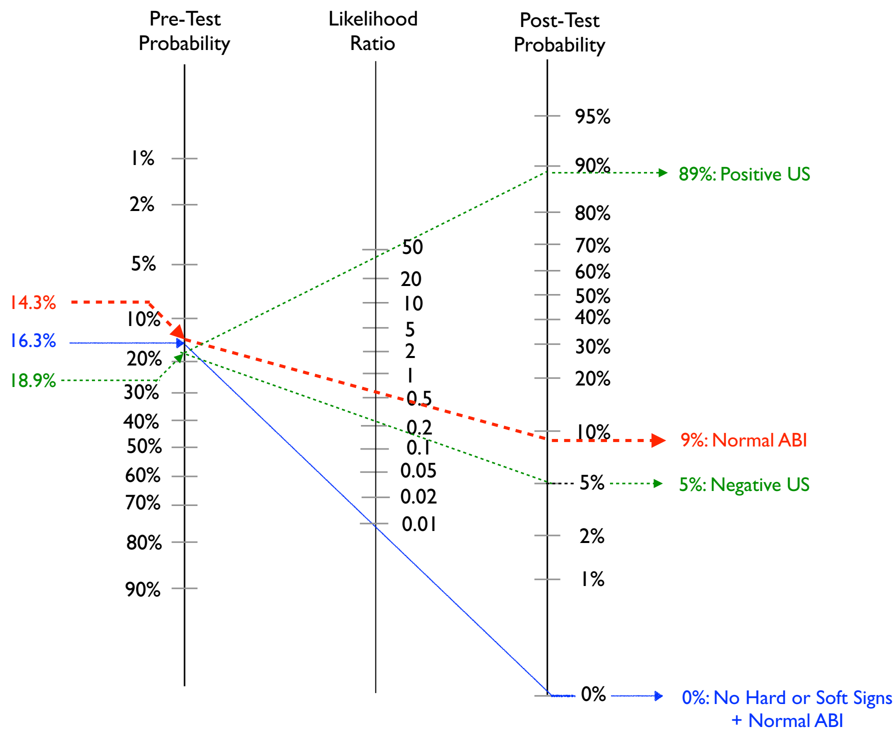

Figure 5. Posttest probabilities using ABI, US, and physical examination any signs with ABI in combination. Pretest probability = weighted arterial injury prevalence in trial groups (US 18.9%, ABI 14.3%, physical examination any signs with ABI 16.3%). ABI = ankle-brachial, brachial-brachial, or wrist-brachial index; US = ultrasonography.

et al.,[28] and Bergstein et al.[30] examined a sample of patients for whom US was performed in addition to the reference test, whereas Kuzniec et al.[31] studied consecutive patients. Anderson et al.[27] used high-resolution B-mode US and did not define an abnormal study, whereas Gagne et al.,[28] Bergstein et al.,[30] and Kuzniec et al.[31] used color-flow duplex examinations and specified sonographic criteria for arterial injury. A radiologist performed image acquisition and interpretation in Anderson et al.,[27] and either a registered vascular technologist or vascular surgery fellow performed image acquisition and interpretation in Bergstein et al.[30] In the other two trials,[28,31] a registered vascular technologist[28,31] acquired the images, but the interpreter in these studies was not reported. In all included studies, the reference standard was catheter angiography. None of the studies reported intra- or inter-rater reliability of their US interpretations.

Performance Characteristics of US

Gagne et al.[28] was excluded from meta-analysis for reasons that have been previously described. Upon meta-analysis of the remaining included studies,[27,30,31] we calculated a LR+ of 35.4 (95% CI = 8.3–151, I^2 = 0%) for positive US, and LR– of 0.24 (95% CI = 0.08 to 0.72, I^2 = 53.6%) for negative US (Table 8, Figure 7). Applying Bayes' theorem, using the weighted prevalence (18.9%) as an estimate of the pretest probability with LR+ of 35.4 and LR– of 0.24 yielded arterial injury posttest probabilities of 89% (95% CI = 84%–93%) after positive US and 5% (95% CI = 4%–7%) following negative US (Figure 5).

Test–Treatment Threshold Estimates

We applied the Pauker and Kassirer test–treatment threshold model[24] to aid the clinician in efficiently and accurately confirming or excluding the diagnosis of arterial injury in patients with PET. This model utilizes the unique performance characteristics of CTA while controlling for the risk of treatment (Rrx) of patients without arterial injury, the risk of the diagnostic test (Rt), and the benefit of treatment (Brx) of patients with arterial injury. In a systematic review and meta-analysis, Jens et al.[18] found CTA to have a sensitivity of 96.2% and specificity 99.2% for the detection of arterial injury. The treatment of arterial injuries may include endovascular techniques such as balloon occlusion, embolization, and stent/stent graft placement or surgery (the criterion standard) depending on the nature of lesion.[33] We defined the risks of treatment without disease (Rrx) as the risks related to vascular intervention or surgery. Patients without arterial injury but exposed to vascular

Table 7
Performance Characteristics of Physical Examination Hard or Soft Signs with Ankle-Brachial Index in Combination

Study	N	Artery Injury Prevalence, % (95% CI)	Sensitivity, % (95% CI)	Specificity, % (95% CI)	LR+ (95% CI)	LR– (95% CI)
Schwartz et al., 1993[25]	469	16.4 (13.8–19.4)	100 (95.0–100)	54.3 (49.3–59.3)	2.18 (1.95–2.43)	0.01 (0.00–0.19)
Inaba et al., 2011[8]	212	16.0 (11.7–21.6)	100 (90.0–100)	87.2 (81.1–91.9)	7.56 (5.09–11.2)	0.02 (0.00–0.26)
Pooled	**1,178**	**16.3 (13.7–19.3)**	**100 (97.0–100)**	**[I^2 = 98.3%]**	**[I^2 = 97.7%]**	**0.01 (0.00–0.10)**

Pooled data are reported when $I^2 \leq 75\%$.
LR = likelihood ratio.

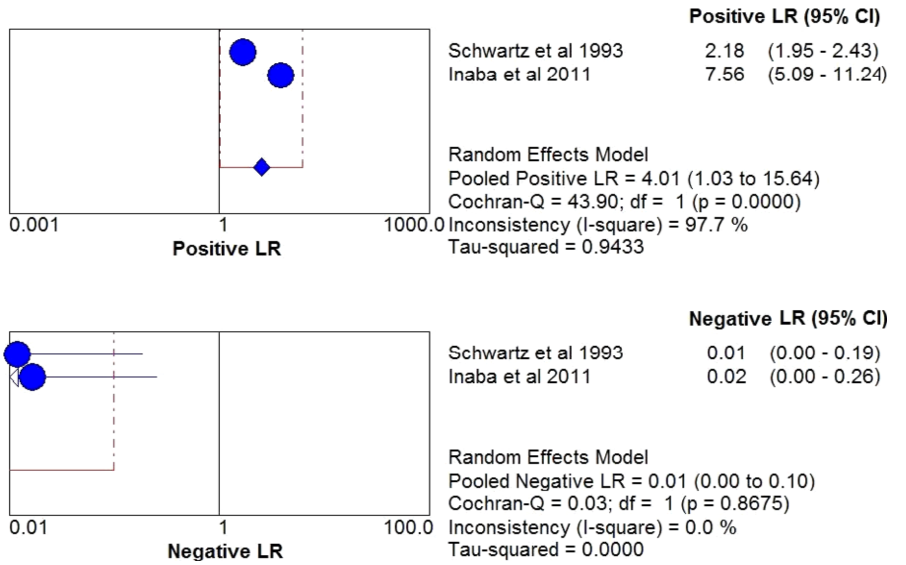

Figure 6. Forest plots for physical examination hard or soft signs with ankle-brachial index in combination. LR = likelihood ratio.

intervention or surgery may suffer the risks of catheter angiography (i.e., arterial thrombosis, pseudoaneurysm),[34] surgery (i.e., wound infection, thromboembolism), and anesthesia (i.e., aspiration syndrome) without any of the intended benefits. Based upon large registry[2,35] and cross-sectional[34] data, we conservatively estimated the Rrx to be 10% (Rrx = 0.10). We judged the risk of the diagnostic test (Rt) to be the lifetime medical radiation–related risk of malignancy attributed to one CTA examination (Rt = 0.0005).[36] Finally, the benefit of treatment (Brx) of patients with arterial injury is limb salvage with functional recovery. The Brx has never been, nor ever will be, tested with randomized, double-blind, placebo-controlled methodology; it would be unethical to study the spontaneous resolution rate of arterial injury (without intervention). Without adequate available evidence, we consulted our local trauma surgery experts and made the assumption that 95% of arterial injuries will benefit from endovascular or operative repair, whereas 5% will resolve without intervention. This would represent an estimate for the benefit of treating arterial injury (Brx = 0.95).

In Figure 8, we illustrate a test–treatment threshold model for US to diagnose arterial injury. The top half of Figure 8 describes the variables and calculations used to produce the testing and treatment thresholds of CTA that are depicted in the graphic below. The testing threshold is depicted as the left-most, open arrow (0.14%). If the posttest probability of US (dotted vertical line) falls to the left the testing threshold (0.14%), then further testing for arterial injury is not warranted, and an alternative diagnosis other than arterial injury should be considered. The treatment threshold for CTA is represented with the right-most, open arrow (72.9%). If the posttest probability of US falls to the right of the treatment threshold (72.9%), further testing is unnecessary, and vascular intervention or surgery may proceed based only upon the results of US. If the posttest probability of US falls in between the testing and treatment

Table 8
Performance Characteristics of Ultrasonography

Study	N	Artery Injury Prevalence, % (95% CI)	Sensitivity, % (95% CI)	Specificity, % (95% CI)	LR+ (95% CI)	LR– (95% CI)
Anderson et al., 1990[27]	23	26.1 (12.3–46.8)	83.3 (35.9–99.6)	100 (80.5–100)	28.3 (1.79–447)	0.22 (0.05–0.91)
Bergstein et al., 1992[30]	75	5.3 (1.7–13.3)	50 (6.8–93.2)	98.6 (92.4–100)	35.5 (4.02–314)	0.51 (0.19–1.35)
Kuzniec et al., 1998[31]	39	41.0 (27.0–56.6)	93.8 (69.8–99.8)	100 (85.2–100)	43.8 (2.81–682)	0.09 (0.02–0.42)
Pooled	**137**	**18.9 (13.2–26.4)**	**84.6 (65.1–95.6)**	**99.1 (95.1–100)**	**35.4 (8.28–151)**	**0.24 (0.08–0.72)**

Pooled data are reported when $I^2 \leq 75\%$.
LR = likelihood ratio.

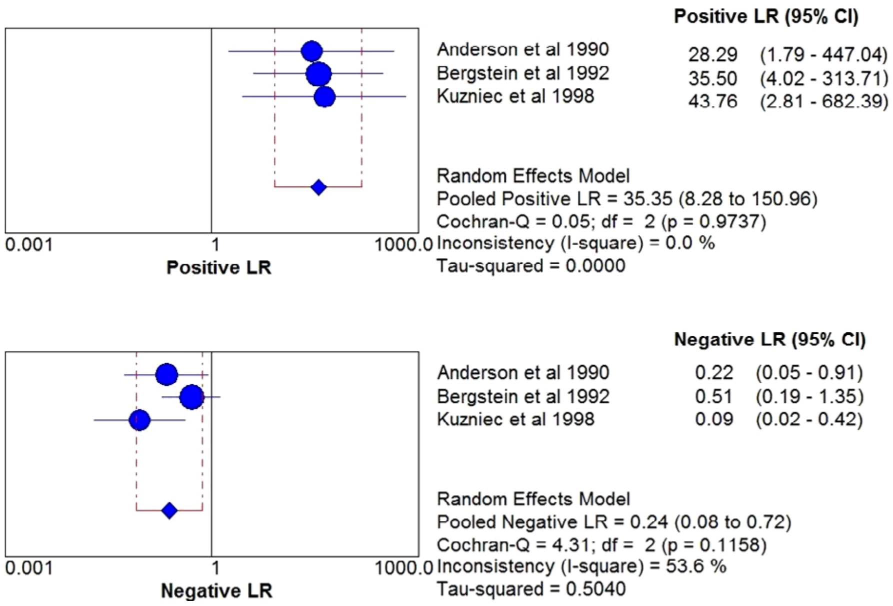

Figure 7. Forest plots for ultrasonography. LR = likelihood ratio.

thresholds, then our model recommends further investigation with CTA.

Applying Bayes' theorem, using the weighted prevalence (18.9%) as an estimate of the pretest probability with LR+ of 35.4 and LR– of 0.24 would lead to arterial injury posttest probabilities of 89% after positive US and 5% following negative US (Figure 5). If US is positive, the probability of arterial injury would increase from 18.9% to 89%, which exceeds the treatment threshold (72.9%); further testing with CTA would not be necessary to confirm arterial injury prior to vascular intervention or surgery (Figure 8). However, even though arterial injury may be diagnosed with positive US, the consulting surgeon may request a pre-procedural CTA to identify venous injuries or fractures or assist in anatomic mapping and planning of the repair. If US is negative, the posttest probability of arterial injury would be reduced from 18.9% to 5% (Figure 5), which although quite low, still exceeds the testing threshold of CTA (0.14%). Our test–treatment threshold model would therefore recommend further testing with CTA to exclude arterial injury (Figure 8).

The test–treatment model presented here is versatile (Appendix A, available as from the author at http://onlinelibrary.wiley.com/doi/10.1111/acem.12878/full), and some variables can be adjusted. For example, we estimated the risk of treatment (Rrx) to be 10%. Assigning a higher Rrx to certain patients based upon clinical judgment will result in an increased treatment threshold, and a more liberal approach to testing may be recommended for those patients. We also estimated the benefit of treatment the (Brx) to be 95%; however, reducing the Brx to as low as 40% will not considerably change the results.

Testing threshold = [(Ppos/nd) x (Rrx) + Rt] ÷ [(Ppos/nd x Rrx) + (Ppos/d x Brx)] = 0.14%

Treatment threshold = [(Pneg/nd) x (Rrx) - Rt] ÷ [(Pneg/nd x Rrx) + (Pneg/d x Brx)] = 72.95%

Ppos/nd = probability of a positive result in patients without disease = 1-specificity = 1-0.992= 0.008

Pneg/nd = probability of a negative result in patients without disease = specificity = 0.992

Rrx = risk of treatment in patients without disease = 0.10

Rt = risk of diagnostic test = 0.0005

Ppos/d = probability of a positive result in patients with disease = sensitivity = 0.962

Pneg/d = probability of a negative result in patients with disease = 1 – sensitivity = 0.038

Brx = benefit of treatment in patients with disease = 0.95

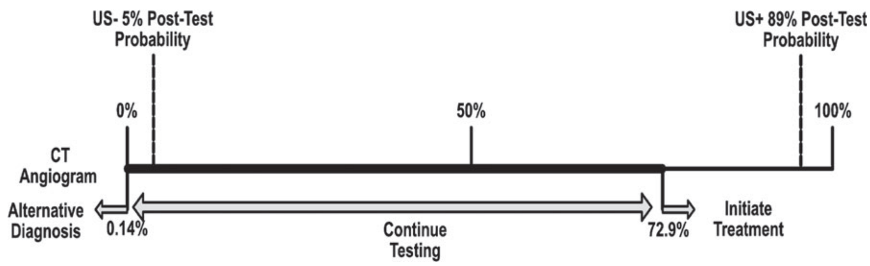

Figure 8. Test–treatment threshold estimates for ultrasonography. US– = negative ultrasonography; US+ = positive ultrasonography.

DISCUSSION

The swift and accurate diagnosis of arterial injury in patients with PET is paramount to prevent morbidity such as amputation and compartment syndrome and occasionally death. In 2012, the EAST updated a practice management guideline[3] for the evaluation and management of penetrating lower extremity trauma. The EAST committee searched the literature for studies published from 1998 to 2011, a narrower date range than that searched in our review (inception to 2016). The EAST used nine trials as the evidentiary basis for the diagnostic section of the guideline.[3] We included Inaba et al.[8] but excluded Lynch and Johansen[7] and Johansen et al.[11] due to insufficient available data. Two trials (Sadjadi et al.[37] and Dennis et al.[10]) did not meet our inclusion criterion of minimum 24-hour observation period for patients who were not evaluated with the reference standard. The remaining four studies examined the utility of CTA for the diagnosis of arterial injury.

The WTA also published a position statement[4] in 2011 that presents an algorithm for the evaluation of the patient with possible peripheral vascular injury. This guideline is based on observational studies and expert opinion; there is no explicit search strategy or criteria for its references, and in contrast to the EAST guideline,[3] its recommendations are not graded. Four studies[25,28–30] that are cited in the WTA guideline[4] to support recommendations for arterial injury diagnosis are also included in our review. The other trials were excluded from our review for various reasons. Miranda et al.[38] focused on knee dislocation injuries. Dennis et al.[9] included only proximity injuries without hard signs. Bynoe et al.,[39] Lynch and Johansen,[7] and Johansen et al.[11] were excluded due to insufficient available data. Finally, we omitted Frykberg et al.,[6] Knudson et al.,[12] Dennis et al.,[10] Sadjadi et al.,[37]and Fry et al.[40] due to an inadequate inpatient observation period for patients who did not undergo the reference standard. The EAST and WTA both assessed the evidence qualitatively to develop their guidelines.[3,4] In comparison, our systematic review and meta-analysis puts forth recommendations that are based on quantitative analysis of the available data.

In our systematic review and meta-analysis, we found that the performance characteristics of the presence of a hard sign after a penetrating extremity injury were too heterogeneous to pool (I^2 = 96.5%; Table 5). This trial heterogeneity of LR+ may be due to 1) the wide spectrum of physical examination findings and associated risks of arterial injury, 2) the varying, somewhat ambiguous definitions of hard and soft signs in clinical practice and study methods, and 3) the inconsistent definitions of hard and soft signs among the individual trials themselves (Table 2). The LR+ ranged from 2.89 to 210, but again, these calculations are fraught with partial verification bias as only patients with physical examination signs of vascular injury went on to reference testing (CTA, catheter angiography, or surgical exploration). Nonetheless, with weighted prevalence (13.8%) as pretest probability, this LR+ range (2.89–210) produced an arterial injury posttest probability of 36% to 98%, which encompasses our estimated treatment threshold (72.9%). Therefore, according to the available, yet inconsistent evidence and through application of our test–treatment threshold model (Figure 8), the decision to first perform further testing or proceed directly to surgery should be based upon clinical judgment. This is consistent with EAST[3] and WTA[4] guidelines. The EAST recommends (level 2) that patients with hard signs of vascular injury (Table 1) should undergo expedient surgical exploration. The guidelines[3,4] further qualify this direction by describing situations (such as shotgun or skeletal injuries) in which hard signs may be present, but timely US[4] or catheter angiography[3,4] may yet serve a purpose for the localization of the lesion. The minor discrepancy between our recommendation and those of the guidelines[3,4] may be due to inconsistency of the definitions of hard and soft signs between the guidelines[3,4] (Table 1) and the trials[8,25,26] (Table 2) that are included in this review.

In our systematic review, the trials[8,25,26] in the physical examination group were also too heterogeneous to combine for absence of hard signs (I^2 = 92.6%; Table 5). Again, the heterogeneity of LR– may be due to the wide spectrum of physical examination findings and associated risks and the varying definitions of hard and soft signs, both in clinical practice and among the individual trials (Table 2). Using weighted prevalence (13.8%) as the pretest probability, the range of LR– (0.08–0.61) resulted in an arterial injury posttest probability of 1% to 11%. This range of posttest probabilities (1%–11%) exceeds the testing threshold (0.14%), so according to our test–treatment threshold model, patients without hard signs should be studied with CTA to rule out arterial injury (Figure 8). In the included studies,[8,25,26] the patients who did not demonstrate hard signs may have had any number of soft signs (Table 2). The incidence of arterial injury in patients with soft signs may range from 3% to 25%, depending on which sign or constellation of signs is present.[3,4] Since none of the studies provided the specific number of extremities with an *individual* soft sign alone, we could not calculate the arterial injury prevalence in patients who demonstrated a *specific* soft sign. Furthermore, there is no prior study of the association of pretest probablities to the various soft signs. Therefore, a soft sign in clinical practice is subject to individual interpretation and assessment of risk/pretest probability. For example, a stab wound to the lateral aspect of the thigh with a nonexpanding hematoma may be lower risk and therefore assigned a lower pretest probability than a gunshot wound to the medial aspect where the femoral artery resides. The patient with the lateral thigh injury may be safely discharged, whereas the patient with the medial thigh wound may benefit from CTA or inpatient observation. With this reasoning in mind, when the injured extremity does not exhibit hard signs, one may use clinical judgment of the risk associated with the soft signs present to determine the need to investigate further with CTA. This recommendation is consistent with EAST[3] (level 2) and WTA[4] guidelines which, although with greater conviction, advise that when hard signs are absent but other physical examination findings (i.e., soft signs) are present, the patient should undergo ABI testing and/or further imaging for possible arterial injury. Once again, the minor discrepancy between our recommendation and those of the guidelines[3,4] may be due to inconsistency of the definitions of hard and soft signs between the guidelines[3,4] (Table 1) and the trials[8,25,26] (Table 2) that are included in this review.

In the ABI studies[8,25,27] that were pooled, the measurements were performed on subjects who demonstrated certain physical examination findings, and as discussed, these findings were inconsistent across the trials (Table 2). The variability of soft signs in patients who were subsequently studied with ABI most likely explains the high heterogeneity (I^2 = 81.7%; Table 6) for abnormal ABI. With the weighted prevalence (14.3%) as pretest probability, the LR+ range (3.1–23) resulted in an arterial injury posttest probability of 34% to 79%. This posttest probability range (34%–79%) spans the treatment threshold (72.9%), so according to our test–treatment threshold model (Figure 8), the decision to proceed directly to vascular intervention or surgery or perform additional testing in patients with abnormal ABI should be based upon clinical judgment.

We calculated a pooled LR– of 0.59 for normal ABI, and using the weighted prevalence (14.3%) for pretest probability, the LR– (0.59) would reduce the arterial injury posttest probability from 14.3% to 9% (Figure 5). This probability following a normal ABI (9%) exceeds the testing threshold of CTA (0.14%), and our model would therefore suggest that patients with soft signs and normal ABI should be further investigated with CTA to rule out arterial injury (Figure 8). Our recommendations with respect to ABI are in agreement with the EAST guideline,[3] which states (level 2) that in the presence of soft signs (Table 1) and/or abnormal ABI, the patient should undergo further imaging to exclude arterial injury. However, we believe it important to reiterate that the assessment of soft signs may be subjective, and not all soft signs may be equal in risk. There may be a patient who has a soft sign that is sufficiently low-risk with a relatively lower pretest probability (i.e., stab wound to lateral thigh with nonexpanding hematoma); if ABI is normal, this patient may be discharged or observed without further imaging. This is an important supposition, as some resource-limited institutions may not have CTA easily available. A more limited approach to imaging is suggested by the WTA algorithm.[4] The WTA advise that when soft signs (Table 1) are present but ABI is normal, the patient may be discharged without imaging.

Since neither the absence of hard signs nor an abnormal ABI was independently capable of excluding arterial injury, we investigated the diagnostic accuracy of physical examination with ABI *in combination* for the exclusion of arterial injury. Inaba et al.[8] and Schwartz et al.[25] examined a sample of patients without *any* signs (hard or soft as defined in each trial) who then underwent ABI testing. For absence of hard and soft signs plus normal ABI, the pooled LR– was 0.01; using weighted prevalence (16.3%) as pretest probability, this resulted in an arterial injury posttest probability of 0% (Figure 5). Therefore, a physical examination with ABI in sequence may be used to rule out an arterial injury. When the physical examination demonstrates neither hard nor soft signs, and the ABI is normal, the patient may be safely discharged without further evaluation. Our findings are in agreement with EAST[3] (level 2) and WTA[4] guidelines that state that patients with *normal* physical examination findings and an ABI greater than or equal to 0.9 may be discharged.

However, there is an important caveat here. The definition of soft sign was different between Inaba et al.,[8] Schwartz et al.[25] (Table 2), and the EAST[3] and WTA[4] guidelines (Table 1). As an example, Inaba et al.[8] and Schwartz et al.[25] did not explicitly classify an injury trajectory that may have crossed the path of a major vessel (proximity) as a soft sign, but the guidelines[3,4] do so. Citing prior investigation,[41] Schwartz et al.[25] did not consider proximity alone to be a good indicator of arterial injury and therefore did not categorize proximity as a soft sign in their trial. So, it may be inferred that in Inaba et al.[8] and Schwartz et al.,[25] a number of the subjects without "any" signs, in fact, had proximity injuries. Actually, Inaba et al.[8] reported that there were 11 patients with proximity injury only who underwent CTA (protocol violations), and all studies were negative for arterial injury. In contrast to Inaba et al.[8] and Schwartz et al.,[25] Gonzalez and Falimirski[26] included *only* patients with proximity injuries; proximity only and absence of hard signs had a LR– of 0.08 to result in an arterial injury posttest probability of 1%. Additionally, the two outlying trials in our review, Nassoura et al.[29] and Gagne et al.,[28] studied patients with only proximity injury and without hard or any other soft signs. In Nassoura et al.,[29] proximity injury and normal ABI had a LR– of 0.28 and an arterial injury posttest probability of 4%. Nassoura et al.[29] further report that only 1.5% of extremities with proximity injury and normal ABI eventually required vascular intervention or surgery. In Gagne et al.,[28] 4% of all extremities with proximity injury required intervention. Gagne et al.[28] studied a sample of 25 injured lower extremities with ABI and reported normal measurements in all; only three extremities had arterial injuries upon catheter angiography, and only one required surgical repair. Similarly, Dennis et al.[9] in a large prospective trial reported an arterial injury prevalence of 5.1% among proximity injuries without hard or any other soft signs, and in comparison, a prevalence of 29.2% among proximity injuries with other soft signs. However, in the entire sample of proximity injuries, regardless of presence or absence of soft signs, Dennis et al.[9] reported that only 2.2% of injuries required surgery at any time, and 86% of arterial injuries that were followed nonoperatively with repeat catheter angiography demonstrated resolution, improvement, or remained unchanged. Finally, Frykberg et al.[42] also prospectively examined proximity injuries and reported 6.3% arterial injury prevalence among proximity injuries alone and 31% among proximity injuries with other soft signs; only 1.3% of the sample ultimately required surgery, and 93% of arterial injuries that were followed with repeat catheter angiography either resolved, improved, or remained unchanged. The qualitative analysis of the results from Gonzalez and Falimirski,[26] Gagne et al.,[28] and Nassoura et al.,[29] with support from other trials,[9,41,42] suggests that the probability of *clinically significant* arterial injury (requiring intervention) in patients with proximity-only injury and a normal ABI is likely to be very low. However, we ultimately did not have sufficient data to calculate the diagnostic power of "proximity" as a soft sign in isolation, so the decision to further test, observe, or discharge these patients should be based upon clinical judgment.

Our systematic review and meta-analysis demonstrated for US a pooled LR+ of 35.4 for a positive test; using weighted prevalence of 18.9% as pretest probability, this resulted in an arterial injury posttest probability of 89% (Figure 5). This exceeds the treatment threshold (72.9%), so if US is positive, our model suggests that the clinician may omit CTA (Figure 8) and avoid further delay prior to vascular intervention or surgery. Again, this is an important finding, as institutions without CTA capability may then rely on US to diagnose arterial injury instead of less accurate evaluations such as physical examination or ABI. The pooled LR– for negative US was 0.24; using weighted prevalence (18.9%) as pretest probability, this yielded an arterial injury posttest probability of 5%. Although this probability is still greater than the test threshold (0.14%), and our model will recommend CTA (Figure 8), the decision to proceed with CTA should be determined on a case-by-case basis and include judgment of the risk commensurate with the particular physical examination findings beforehand. The clinician should also appreciate the limitations of US to detect lesions in the axilla and bifurcated arteries.[30] In a patient with PET who demonstrates what may be considered a soft sign with an associated low pretest probability (i.e., stab wound to lateral thigh with nonexpanding hematoma), negative US may be sufficient to exclude arterial injury. Ultrasonography may also prove useful as an additional, if not substituted, diagnostic test as CTA may be limited by artifact due to bullet, shrapnel, or bone fragments in up to 8% of patients with PET.[8] Our recommendations are consistent with the guidelines.[3,4] The WTA guideline,[4] while acknowledging its limitations, suggests that duplex US is an appropriate diagnostic modality on the same level as CTA and catheter angiography for the diagnosis of arterial injury in patients with PET. The EAST guideline[3] addresses US with less certainty. The EAST states (level 3) that the role of US in the confirmation or exclusion of arterial injury is not well defined but may be useful in the evaluation of proximity injuries or wounds with soft signs of vascular injury.

Catheter angiography is a relatively time-consuming and invasive procedure and requires specialized personnel that may not be readily available at all hours in many institutions. Complication rates of catheter angiography have been reported to be as high as 9% and include hematoma, arterial thrombosis, and pseudoaneurysm.[34] In contrast, CTA is a noninvasive, rapid, and readily obtainable imaging modality with efficacy that is comparable to traditional catheter angiography. CTA can rapidly identify arterial injuries including pseudoaneurysm, active arterial hemorrhage, arteriovenous fistulae, occlusion, intimal injury, or vasospasm,[43] and it can also detect associated musculoskeletal injuries. The EAST guideline[3] states (level 1) that CTA may be the primary diagnostic test for the evaluation of penetrating lower-extremity arterial injury. We estimated the risk of CTA to be very low (0.05%) after considering the medical radiation–related risk of malignancy. So, when life or limb is considered to be at stake, this begs the question, why not simply perform CTA on all patients with PET who do not need immediate surgical exploration? First, the non-negligible radiation risk may be relatively more pronounced in the typically young[44] PET patient, as there are more expected years of life for the consequences of radiation exposure to manifest. Second, there are the unaccounted-for consequences of finding lesions of uncertain significance. CTA may find occult, self-limited injuries[10,45] such as intimal flap, focal narrowing, and small pseudoaneurysm. The discovery of these lesions may, at times, prompt additional investigation with catheter angiography or operative exploration and assumption of their associated, greater risks. In addition, non-judicious use of CTA may more frequently discover incidental abnormalities, particularly when the test is applied to low-risk patients (in whom arterial injury prevalence may be low). This may result in exposure to nonbeneficial downstream testing, which, in turn, may lead to inappropriate treatment related to misdiagnosis and the overdiagnosis of common but unimportant findings.[46,47] Finally, although CTA is relatively low in cost, its non–evidence-based use may deplete the limited resources of hospitals in urban areas or high-conflict regions where patients with penetrating injuries are frequently encountered. Ultrasonography may be an acceptable, even lower-cost alternative in certain low-risk patients, and a selective approach to CTA has shown to greatly reduce the expense per patient.[37]

Implications for Future Research

Our systematic review, along with its findings, also illustrates that there is significant need for further study of patients with PET. The professional organizations in both emergency medicine and trauma surgery should reach consensus on objective definitions of hard and soft signs of vascular injury for clinical practice, education, and research. Prospective trials that follow injuries with soft signs nonoperatively with serial CTA at regular intervals may help determine the characteristics of arterial injuries that will require intervention or resolve spontaneously; these data may then help to define which lesions discovered by CTA are clinical significant. Additional prospective, descriptive studies with objectively defined soft signs may help to better risk stratify the soft signs (i.e., proximity only vs. proximity with stable hematoma). Similarly designed trials that involve multiple regression analysis of specific, clearly defined signs along with other patient characteristics may assist in the development of clinical decision tools. Future reliability studies that evaluate the diagnostic utility of physical examination, ABI, and US should analyze patient-centric outcomes and adhere to the STARD reporting guidelines[48] to make more transparent the potential for bias. Prospective study should also attempt to clarify the utility of screening ABI alone in ruling out clinically significant arterial injury in patients with specific, clearly defined, soft signs (i.e., proximity) of vascular injury. Randomized trials should examine the diagnostic accuracy and cost-effectiveness of serial ABIs with observation versus CTA alone in patients with soft signs; this study would be most helpful in clinical settings where CTA, catheter angiography, or trauma expertise may not be available, and patients would require transfer for such interventions and level of care. In all potential studies, investigators should attempt to assess the harms of both under- and overtesting whenever possible. Van Haren et al.[49] has suggested that continuous, bilateral near-infrared spectroscopy may detect perfusion abnormalities to reliably identify vascular injury, and larger such studies may demonstrate distinct advantages of this modality over serial ABIs. Additional, prospective trials of contemporary US, both formal examinations by radiologists and point-of-care testing by ED clinicians, may more definitively demonstrate its value in ruling out arterial injury in the patient who is exhibiting specific, clearly defined soft signs. The use of current US devices, which are more technologically advanced than those used in the trials in our review, may be accurate enough to exclude arterial injury or at least more definitively justify the substitution of US for CTA and its associated risks. Finally, our systematic review and meta-analysis recommends clinical judgment in many situations, so there will be the possibility of alternative management plans with associated risk/benefit analyses. There will be opportunity to both engage in shared decision-making with PET patients and study its efficacy in reducing healthcare cost without evidence of harm.[50]

LIMITATIONS

Many of the trials in our review were subject to partial and differential verification bias. The patients who were considered low-risk were often observed and did not undergo catheter angiography or CTA; therefore, occult arterial injuries may have been present without identification. A significant proportion of these low-risk patients were lost to follow-up when reported.[25] Loss to follow-up can misdiagnose delayed arterial injury and introduce further bias. This bias may alter the calculated test characteristics; if all patients who were lost to follow-up had an injury, this would reduce the sensitivity and specificity by altering the proportion of true and false negatives. We excluded all studies in languages other than English, which may result in language bias; however, language restriction in systematic reviews and meta-analyses in medicine has not been shown to result in bias.[51] Data were unavailable from some trials for analysis, because either the original investigators could not be contacted or they could not provide the raw data. We did not have access to patient-level data for all included trials, so we could not account for individual effects of injury severity, patient age, or comorbidities or calculate the index test performance characteristics for diagnosis of clinically significant arterial injuries—those that required vascular intervention or operative repair. All but one study[8] used catheter angiography as a reference standard, and based upon recent evidence[8,18] and current guidelines,[3,4] we made the assumption that CTA was equivalent to catheter angiography. This premise may introduce the issue of external validity, as our review offers recommendations for CTA based largely upon data from catheter angiography studies. In our analysis, we did not measure the rates of other outcomes such as venous injury or thrombosis, soft tissue infection, or long-term vascular insufficiency. However, these complications, although significant in that they may require treatment, do not typically need emergent vascular intervention or operative repair. We used rigorous inclusion and exclusion criteria that sometimes resulted in smaller sample sizes and point estimates with large CIs. This was most evident with US for which the group had a combined sample of 173 extremities. Therefore, the results from analysis of this group may not be generalizable. On the other hand, the included studies[27,28,30,31] of US were conducted in the 1990s, and there have since been technologic advances. This may result in temporal bias,[52] and US may be more accurate in present-day practice and own superior performance characteristics than what we report in our meta-analysis.

CONCLUSIONS

In patients with penetrating extremity trauma, positive ultrasonography may obviate CT angiography for the diagnosis of arterial injury. In patients with a normal physical examination (no hard or soft signs) and a normal ankle-brachial index, an arterial injury can be ruled out. However, a normal ankle-brachial index or negative ultrasonography cannot independently exclude arterial injury. Finally, there was high study heterogeneity likely due in part to inconsistent trial definitions of vascular injury signs, and we cannot make management recommendations when hard signs are present or absent or when ankle-brachial index is abnormal. In these situations, one should use clinical judgment to determine the need for further observation, CT angiography or catheter angiography, or surgical exploration.

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Supporting Information

The following supporting information is available in the online version of this paper available at http://onlinelibrary.wiley.com/doi/10.1111/acem.13227/full

Data Supplement S1. Measurement of the Systolic Pressure Index.

Data Supplement S2. Database Search Strategies.