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A systematic review showing the lack of diagnostic criteria and tools developed for lower-limb cellulitis*

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Summary

Background Cellulitis can be a difficult diagnosis to make. Furthermore, 31% of patients admitted from the emergency department with suspected lower-limb cellulitis have been misdiagnosed, with incorrect treatment potentially resulting in avoidable hospital admission and the prescription of unnecessary antibiotics.

Objectives We sought to identify diagnostic criteria or tools that have been developed for lower-limb cellulitis.

Methods We conducted a systematic review using Ovid MEDLINE and Embase databases in May 2018, with the aim of describing diagnostic criteria and tools developed for lower-limb cellulitis, and we assessed the quality of the studies identified using the Quality Assessment of Diagnostic Accuracy Studies-2 tool. We included all types of study that described diagnostic criteria or tools.

Results Eight observational studies were included. Five studies examined biochemical markers, two studies assessed imaging and one study developed a diagnostic decision model. All eight studies were considered to have a high risk for bias in at least one domain. The quantity and quality of available data was low and results could not be pooled owing to the heterogeneity of the findings.

Conclusions There is a lack of high-quality publications describing criteria or tools for diagnosing lower-limb cellulitis. Future studies using prospective designs, validated in both primary and secondary care settings, are needed.

What's already known about this topic?

- Diagnosing lower-limb cellulitis on first presentation is challenging.
- Approximately one in three patients admitted from the emergency department with suspected lower-limb cellulitis do not have cellulitis and are given another diagnosis on discharge. Consequently, this results in potentially avoidable hospital admissions and the prescription of unnecessary antibiotics.
- There are no diagnostic criteria available for lower-limb cellulitis in the U.K.

What does this study add?

- This systematic review has identified a key research gap in the diagnosis of lower-limb cellulitis.
- There is a current lack of robustly developed and validated diagnostic criteria or tools for use in clinical practice.

Cellulitis is an acute bacterial infection of the dermis and associated subcutaneous tissue, with 60% of cases affecting the lower limb.[1] Erysipelas is a form of cellulitis that presents with more marked superficial inflammation.[2]

The diagnosis of cellulitis can be challenging, with 31% of patients who present with suspected lower-limb cellulitis in the emergency department (ED) subsequently being given a diagnosis other than cellulitis.[3] Routine biochemical and haematological blood tests and blood cultures are not specific for cellulitis.[4] This results in avoidable hospital admissions and unnecessary prescriptions of antibiotics.[5] Definitive diagnostic criteria could potentially improve clinical care and also improve the validity of clinical research on cellulitis by ensuring appropriate case definition.[6] However, there are currently no agreed diagnostic criteria for cellulitis.

Patients with cellulitis commonly present to primary care services or the ED.[7] A recent U.K. cellulitis research priority setting partnership ranked questions on 'diagnostic criteria' as important for future cellulitis research.[8]

The aim of this systematic review was to identify and conduct a critical appraisal of the quality of studies that have developed or validated diagnostic criteria or tools for lower-limb cellulitis.

We define diagnostic criteria or tools as the inclusion of a minimum of one variable that has been tested against at least one clinical feature. In this paper, 'cellulitis' refers to lower-limb cellulitis only. Lower-limb erysipelas is included as it is clinically indistinguishable from cellulitis.

A preliminary search found no previous systematic reviews that investigated the development or validation of diagnostic criteria or tools for cellulitis.

Materials and methods

Protocol and registration

This systematic review was conducted and reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement,[9] with additional reference to the Cochrane Handbook for Diagnostic Test Accuracy Reviews.[10] The protocol was registered with PROSPERO (http://www.crd.york.ac.uk/PROSPERO, record CRD42017080466, November 2017).

Objectives

The primary objective for this review was to identify and describe diagnostic criteria and tools that have been developed for lower-limb cellulitis. The secondary objective was to assess the quality of the studies where diagnostic criteria or tools were developed.

Eligibility criteria

Studies including patients with lower-limb cellulitis or erysipelas in primary and secondary care, which used diagnostic criteria or tools for diagnosis, were included.

Inclusion criteria

The following inclusion criteria were applied: any study type that used diagnostic criteria or tools, in any language, involving patients of any age, sex or ethnicity, who had lower-limb cellulitis or erysipelas.

Exclusion criteria

The following articles were excluded: animal studies; laboratory *in vitro* studies; literature and systematic review articles; expert opinions; conference abstracts; articles that included only patients with nonlower-limb cellulitis; articles where the site of cellulitis or erysipelas was not clear; articles where data from lower-limb cellulitis or erysipelas could not be separated; articles that used tools to determine ethology; case series with < 20 patients or those that included < 10 patients with lower-limb cellulitis or erysipelas.

Database and searches

The following databases were searched on 25 October 2017: Ovid MEDLINE In-Process & Non-Indexed Citations and Ovid MEDLINE (1946 to present), Ovid Embase (1980–2017), the Cochrane Library and Web of Science Core Collection. An updated search on 22 May 2018 was also undertaken in all the databases in order to ensure that the results were up-to-date.

Search strategies for these databases were developed with an information specialist (D.G.) and in consultation with a cellulitis expert (N.J.L.). Concepts were developed: 'cellulitis', 'diagnosis' and 'criteria', with controlled vocabulary (Medical Subject Headings terms and Emtree subject headings) and free-text headings (Table 1). National Institute for Health and Care Excellence Evidence was also searched using the term 'cellulitis'.

For grey literature, the first 100 articles (sorted by relevance) on Google Scholar retrieved using the search term 'diagnostic criteria for cellulitis' were included.

The reference lists of all articles selected for critical appraisal were screened for additional studies.

Study selection and data extraction

Following the searches, all citations were uploaded to Covidence (2018) online systematic review management software,[11] with duplicates removed by one reviewer (M.P.). Title and abstract screening, full-text screening and data extraction were conducted by independent reviewers (M.P. and S.L./R.K.A.) using predefined templates. Any disagreements between reviewers that arose were resolved through discussion, or with another independent reviewer (K.S.T., J.K. or N.J.L.). Data items sought at the data extraction stage included study aim, type, population, criteria, funding, sample size, index test, reference test and key findings.

Table 1 Search terms used in each database

Database	Search terms
Ovid MEDLINE	1. diagnos$.mp. 2. differentiat$.mp. 3. discriminat$.mp. 4. determinin$.mp. 5. confirmat$.mp. 6. ascertainment.mp. 7. detect$.mp. 8. characteris$.mp. 9. characteriz$.mp. 10. identification.mp. 11. identify.mp. 12. exp diagnosis/ 13. exp diagnostic imaging/ 14. or/1-13 15. criteria.mp. 16. criterion.mp. 17. classification.mp. 18. clinical feature.mp. 19. clinical features.mp. 20. test$.mp. 21. tool$.mp. 22. imag $.mp. 23. assay$.mp. 24. accura$.mp. 25. validat$.mp. 26. exp reproducibility of results/ 27. reproducibility.mp. 28. exp validation studies/ 29. exp validation studies as topic/ 30. exp sensitivity and specificity/ 31. sensitivity.mp. 32. specificity.mp. 33. exp predictive value of tests/ 34. predictive.mp. 35. or/15-34 36. and/14 and 35 37. exp diagnostic test, routine/ 38. diagnostic feature.mp. 39. diagnostic features.mp. 40. exp biomarkers/ 41. biomarker$.mp. 42. marker$.mp. 43. or/37-42 44. or/36 or 43 45. exp cellulitis/ 46. cellulitis.mp. 47. exp erysipelas/ 48. erysipelas.mp. 49. or/45-48 50. and/44 and 49
Ovid EMBASE	1. diagnos$.mp. 2. differentiat$.mp. 3. discriminat$.mp. 4. determinin$.mp. 5. confirmat$.mp. 6. ascertainment.mp. 7. detect$.mp. 8. characteris$.mp. 9. characteriz$.mp. 10. identification.mp. 11. identify.mp. 12. exp diagnosis/ 13. exp diagnostic imaging/ 14. or/1-13 15. criteria.mp. 16. criterion.mp. 17. classification.mp. 18. clinical feature.mp. 19. clinical features.mp. 20. test$.mp. 21. tool$.mp. 22. imag $.mp. 23. exp assay/ 24. accura*.mp. 25. exp reproducibility/ 26. reproducibility.mp. 27. exp validation study/ 28. validation studies as topic.mp. 29. validat*.mp. 30. exp ''sensitivity and specificity''/ 31. sensitivity.mp. 32. specificity.mp. 33. exp predictive value/ 34. predictive.mp. 35. or/15-34 36. and/14 and 35 37. exp diagnostic test 38. diagnostic feature.mp. 39. diagnostic features.mp. 40. exp biological marker/ 41. biomarker$.mp. 42. exp marker/ 43. marker$.mp. 44. or/37-43 45. or/36 or 44 46. exp cellulitis/ 47. cellulitis.mp. 48. exp erysipelas/ 49. erysipelas.mp. 50. or/46-49 51. and/45 and 50
Cochrane Database of Systematic Reviews	1.diagnos* 2. differentiat* 3. discriminat* 4. determinin* 5. confirmat* 6. "ascertainment" 7. detect* 8. characteris* 9. characteriz* 10. "identification" 11. "identify" 12. MeSH descriptor: [Diagnosis] explode all trees 13. MeSH descriptor: [Diagnostic Imaging] explode all trees 14. #1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13 15. "criteria" 16. "criterion" 17. MeSH descriptor: [Classification] explode all trees 18. "classification" 19. "clinical feature" 20. "clinical features" 21. test* 22. tool* 23. imag* 24. "assay" 25. accura* 26. MeSH descriptor: [Reproducibility of Results] explode all trees 27. "reproducibility" 28. MeSH descriptor: [Validation Studies as Topic] explode all trees 29. "validation studies" 30. valid* 31. MeSH descriptor: [Sensitivity and Specificity] explode all trees 32. "sensitivity" 33. "specificity" 34. "predictive" 35. #15 or #16 or #17 or #18 or #19 or #20 or #21 or #22 or #23 or #24 or #25 or #26 or #27 or #28 or #29 or #30 or #31 or #32 or #33 or #34 36. #14 and #35 37. MeSH descriptor: [Diagnostic Tests, Routine] explode all trees 38. "diagnostic feature" 39. "diagnostic features" 40. MeSH descriptor: [Biomarkers] explode all trees 41. biomarker* 42. marker* 43. #37 or #38 or #39 or #40 or #41 or#42 44. #36 or #43 45. MeSH descriptor: [Cellulitis] explode all trees 46. "cellulitis" 47. MeSH descriptor: [Erysipelas] explode all trees 48. "erysipelas" 49. #45 or #46 or #47 or #48 50. #44 and #49
Web of Science Core Collection	1.TS = diagnos* 2. TS = differentiat* 3. TS = discriminat* 4. TS = determinin* 5. TS = confirmat* 6. TS = ascertainment 7. TS = detect* 8. TS = characteris* 9. TS = characteriz* 10. TS = identification 11. TS = identify 12. #1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 13. TS = criterion 14. TS = classification 15. TS = "clinical feature" 16. TS = "clinical features" 17. TS = test* 18. TS = tool* 19. TS = imag* 20. TS = assay 21. TS = accura* 22. TS = reproducibility 23. TS = valid* 24. TS = "validation studies" 25. TS = sensitivity 26. TS = specificity 27. TS = predictive 28. #13 or #14 or #15 or #16 or#17 or#18 or#19 or #20 or #21 or #22 or#23 or #24 or #25 or #26 or #27 29. #12 and #28 30. TS = "diagnostic features" 31. TS = "diagnostic feature" 32. TS = biomarker* 33. TS = marker* 34. #30 or #31 or #32 or #33 35. #29 or #34 36. TS = cellulitis 37. TS = erysipelas 38. #36 or #37 39. #35 and #38

Evidence synthesis and risk of bias assessment

All included studies were described in a narrative synthesis. To evaluate the methodological quality, all studies were assessed by two reviewers (M.P. and R.K.A.) using signalling questions in the Quality Assessment of Diagnostic Accuracy Studies-2 tool,[12] with disagreements resolved by a third reviewer (S.I.L. or E.B.-T.). If the information was not clearly provided in the study, then the reviewers assessed the signalling question as 'unclear'.

For each domain, studies were judged as 'low risk' if all signalling questions were answered 'yes', 'high risk' if the answer to at least one signalling question was 'no', or 'unclear' in all other cases.[12]

Results

Study selection

The PRISMA flowchart shows the results of the complete search (Fig. 1). A total of 98 papers were included for full-text screening.[5,13–109] Of these, 90 papers were subsequently excluded,[5,21–109] including 20 studies that did not specify the site of cellulitis[5,37,45,46,49,50,52,63,69,70,72,78,81,91,93,95,97,100,102,109] and

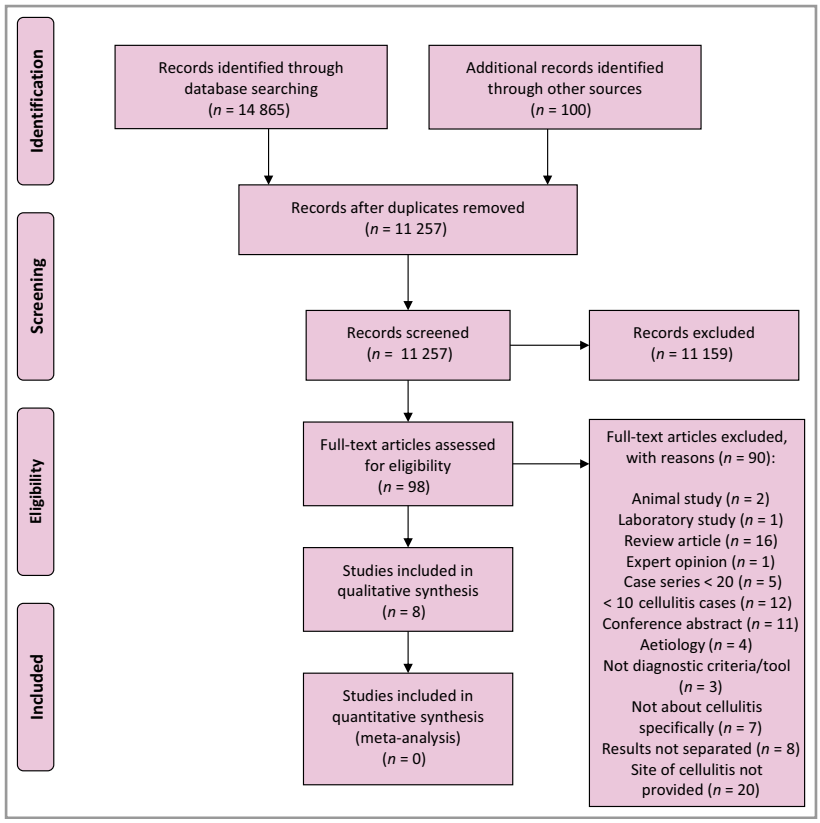

Fig 1. Preferred reporting items for systematic reviews and meta-analyses flowchart of literature search and study selection.

eight studies that did not separate the results of lower-limb cellulitis from other sites.[26,29,55,87,90,98,99,107] Eight studies were included for data extraction.[13–20]

Study characteristics

The characteristics of all eight included studies are summarized in Table 2. Raff *et al.* explored lower-limb cellulitis as the main pathology.[18] Seven studies included patients with lower-limb cellulitis as a comparison group, in which cellulitis and other diagnoses were compared.[13–17,19,20]

Six studies were case–control studies,[13–16,19,20] one study was a cohort study[17] and there was one cross-sectional study.[18] The most common setting was the ED (three studies).[17–20] The studies were conducted in six different countries. Kato *et al.* did not include exclusion criteria.[14]

Reference tests

The reference test for cellulitis was a clinical diagnosis in seven studies,[14–20] with a bone scan used by Fleischer *et al.*[13] However, only Rabuka *et al.* clearly stated the specialty of the physician who made the cellulitis diagnosis.[17] Two studies followed up patients for up to 30 days in order to determine the final diagnosis.[18,19]

Index tests

Studies where cellulitis was the main pathology

Predictive score In a study to compare cellulitis with pseudocellulitis, Raff *et al.* developed an ALT-70 score (7 points) that assessed the following: asymmetry (unilateral involvement, 3 points); leucocytosis (white blood cell count $\geq$ 10 000 μL^{-1}, 1 point); tachycardia (heart rate $\geq$ 90 beats per minute, 1 point); and age $\geq$ 70 years (2 points).[18] An ALT-70 score below 3 had a > 83·3% likelihood of pseudocellulitis – an alternative diagnosis to cellulitis, and a score above 4 had a > 82·2% likelihood of cellulitis.[18]

Studies where cellulitis was used as a comparator

Clinical features One study comparing cellulitis and osteomyelitis among patients with diabetes found that a temperature higher than 37·2 °C was predictive of osteomyelitis;[13] however, Malabu *et al.* found no significant differences in clinical parameters between these groups.[15]

Rabuka *et al.* showed that distinct margins of erythema were seen in six (8%) patients with cellulitis vs. 0 (0%) in patients with deep vein thrombosis (DVT) ($P = 0{\cdot}008$).[17] However, when comparing erysipelas with DVT, Rast *et al.*

Table 2 Characteristics of the eight included studies

Author, year	Country, setting	Years of study	Study type	Diagnoses explored in the study	Funding source	Number of patients analysed	Mean age of patients with cellulitis, years	Number of male patients with cellulitis patients, n (%)	Index test	Reference test for cellulitis	Timeframe for follow-up
Raff *et al.*, 2017[18]	U.S.A., emergency department (single centre)	2010–2012	Cross-sectional	Cellulitis and pseudocellulitis	None stated	259; 180 cellulitis and 79 with pseudocellulitis	63	78 (43)	ALT-70	Clinical diagnosis by ED physician or admitting team	30 days post-discharge
Fleischer *et al.*, 2009[13]	U.S.A., podiatric medicine (single centre)	2002–2006	Case–control	Osteomyelitis and cellulitis	None stated	54; 20 cellulitis and 34 osteomyelitis	62 (whole population)	44 (81) (whole population)	30 clinical and laboratory characteristics	Bone specimen and technetium scan (unclear who made the diagnosis)	No follow-up
Kato *et al.*, 2017[14]	Japan, department of dermatology (single centre)	2010–2014	Case–control	Necrotizing fasciitis and cellulitis	None stated	18; 16 cellulitis, 2 necrotizing fasciitis	Not available for cellulitis patients	Not available for cellulitis patients	LRINEC, CK, PCT	Clinical diagnosis (unclear who made the diagnosis)	No follow-up
Malabu *et al.*, 2007[15]	Saudi Arabia, department of medicine (single centre)	2005	Case–control	Osteomyelitis and cellulitis	None stated	43; 21 with cellulitis and 22 with osteomyelitis	56	12 (57)	ESR, haematocrit, haemoglobin, platelet count, red cell width, WBC	Clinical diagnosis (unclear who made the diagnosis)	No follow-up
Pyo *et al.*, 2017[16]	South Korea, division of rheumatology (single centre)	2010–2015	Case–control	Gout and cellulitis	Korean health industry development institute	367; 184 with acute gout and 183 with cellulitis	61	126 (69)	DNI	Clinical diagnosis (unclear who made the diagnosis)	No follow-up
Rabuka *et al.*, 2003[17]	Canada, emergency department (single centre)	1995–1998	Cohort	DVT and cellulitis	None stated	109; 19 DVT, 72 cellulitis, 18 other	71 (for cellulitis/patients with DVT)	37 (41)	Duplex ultrasound scan	Clinical diagnosis by ED physician	No follow-up
Rast *et al.*, 2015[19]	Switzerland, emergency department (single centre)	2013–2014	Case–control	DVT and erysipelas	Goldschmidt Jacobson Foundation, The Swiss National Science Foundation, The Kantonsspital Aarau	48; 31 erysipelas and 17 with DVT	31	18 (58)	PCT, CRP, WBC	Clinical diagnosis by treating physician	30-day telephone follow-up
Shin *et al.*, 2013[20]	South Korea, department of radiology (single centre)	2006–2010	Case–control	Lymphoedema, cellulitis and generalized oedema	None stated	44; 11 with cellulitis, 19 with lymphoedema and 14 with generalized oedema	63	5 (45)	CT scan	Clinical diagnosis (unclear who made the diagnosis)	No follow-up

LRINEC, The Laboratory Risk Indicator for Necrotizing Fasciitis; CK, creatine kinase; PCT, procalcitonin; ESR, erythrocyte sedimentation rate; WBC, white cell count; DNI, delta neutrophil index; ALT-70, asymmetry, leucocytosis, tachycardia, age > 70 years; CRP, C-reactive protein; DVT, deep vein thrombosis; ED, emergency department; CT, computed tomography.

found no significant differences between any physical signs.[19]

Biochemical and haematological tests In a study comparing cellulitis with acute gout, delta neutrophil index (immature granulocyte count) > 1·7% was the only independent factor for predicting cellulitis (P = 0·002), compared with white blood cell (WBC) count (P = 0·41), C-reactive protein (CRP) (P = 0·277) and procalcitonin (PCT) (P = 0·122).[16] Creatine kinase (CK) was significantly higher in all cases of necrotizing fasciitis (NF) compared with cellulitis.[14]

Malabu *et al.* found that in patients with diabetes, haemoglobin (P < 0·0001) and haematocrit (P < 0·0001) were higher in patients with cellulitis than in patients with osteomyelitis.[15] However, erythrocyte sedimentation rate (ESR) (P < 0·001),[13,15] CRP (P < 0·001),[13] platelet count (P < 0·01),[15] WBC (P < 0·05)[15] and red cell width (P < 0·05)[15] were higher in patients with osteomyelitis than in patients with cellulitis.[15]

In one study, PCT concentrations in patients with erysipelas were compared with PCT concentrations in patients with DVT.[19] Patients with erysipelas had significantly higher concentrations of PCT (P = 0·001). At a PCT threshold of > 0·25 μg L^{-1}, the specificity and positive predictive value for erysipelas was 100%. No significant differences were seen between the two groups with regard to CRP concentrations (P = 0·20) and WBC counts (P = 0·14).[19]

In contrast, Rabuka *et al.* found a raised WBC in 21·3% of patients with cellulitis vs. 50% of patients with DVT (P = 0·038).[17] This study also found that CK was higher in the cellulitis group compared with the DVT group.[17]

Imaging In a study comparing cellulitis with lymphoedema using computed tomography (CT) scanning, Shin *et al.* found specific features that were more frequently associated with cellulitis.[20] These features included fluid collection (P = 0·009), fascial enhancement (P = 0·043), inguinal lymph node enlargement at the affected side (P < 0·001) and inguinal lymph node medullary fat obliteration (P < 0·001).

Rabuka *et al.* examined ultrasound imaging in patients with a presentation suggestive of cellulitis, with 72 patients (80%) diagnosed with cellulitis after having a negative duplex scan.[17]

Methodological quality

Risk of bias

The risk of bias for patient selection was high for all eight studies; six used a case–control method[13–16,19,20] and the exclusion criteria were not deemed appropriate in two studies as they excluded patients who were more difficult to diagnose (Table 3 and Fig. 2).[17,18] The study by Shin *et al.* had a low risk of bias for the index test, as it included a prespecified threshold,[20] whereas the other seven studies did not.[13–19] The reference standard used in the study by Rabuka *et al.* was considered high risk as some patients received the reference test after the index test,[17] thereby increasing the risk of observer bias. The risk was unclear in the remaining seven studies as it was not possible to determine whether the diagnosis of cellulitis was accurate. The flow of timing was unclear in seven studies,[14–20] as it was not stated whether all the patients received the same reference standard test. The flow of timing described in the study by Fleischer *et al.* was considered high risk as not all the patients were analysed.[13]

Concerns regarding applicability

With regard to patient selection and reference standard applicability, all eight studies included patients who had already been diagnosed with cellulitis and we cannot definitively state that the correct diagnosis had been made. However, five studies were high risk for patient selection bias as they included either a rare differential diagnosis for cellulitis, i.e. osteomyelitis and NF,[13–15] or included only patients with initially suspected DVT.[17,20] The index test in four studies was judged to be high risk; two studies included only investigations for diabetic foot ulcers[13,15] and two studies included imaging for suspected DVT.[17,20]

Table 3 Risk of bias assessment using the Quality Assessment of Diagnostic Accuracy Studies-2 diagnostic accuracy critical appraisal tool showing risk of bias for each domain for individual studies

	Risk of bias				Concerns regarding applicability		
Study	Patient selection	Index test	Reference standard	Patient flow and timing	Patient selection	Index test	Reference standard
Fleischer *et al.*[13]	High	High	Unclear	High	High	High	Unclear
Kato *et al.*[14]	High	High	Unclear	Unclear	High	Low	Unclear
Malabu *et al.*[15]	High	High	Unclear	Unclear	High	High	Unclear
Pyo *et al.*[16]	High	High	Unclear	Unclear	Unclear	Low	Unclear
Rabuka *et al.*[17]	High	High	High	Unclear	High	High	Unclear
Raff *et al.*[18]	High	High	Unclear	Unclear	Unclear	Low	Unclear
Rast *et al.*[19]	High	High	Unclear	Unclear	Unclear	Low	Unclear
Shin *et al.*[20]	High	Low	Unclear	Unclear	High	High	Unclear

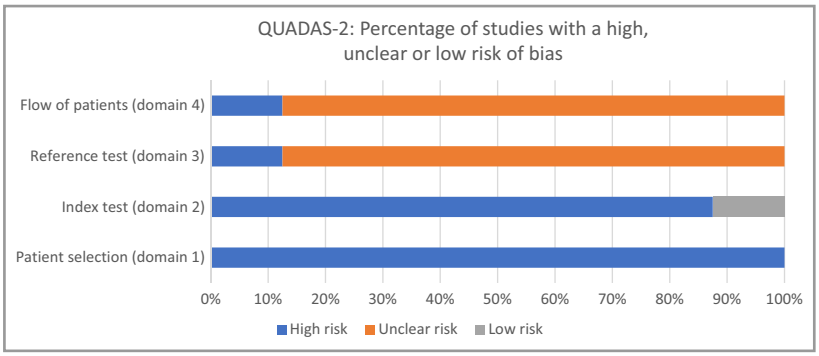

Fig 2. Graph showing the percentage of studies with a low, high or unclear risk of bias for each of the four domains. QUADAS, Quality Assessment of Diagnostic Accuracy Studies.

Excluded studies

Of the excluded studies, 20 did not specify the site of cellulitis. Of these, David *et al.* developed a visually based computerized diagnostic decision support system.[5] Pallin *et al.* studied PCT and HLA-DQA1 expression,[81] Kini *et al.* investigated ESR[52] and three other studies examined the Laboratory Risk Indicator for Necrotizing Fasciitis (LRINEC) score.[63,78,109] Six studies explored radio nucleotide or bone imaging,[37,45,69,70,93,102] five examined magnetic resonance imaging (MRI)[49,50,91,95,97] and two considered ultrasound imaging in the paediatric setting.[46,72] Smirnova *et al.* investigated antibodies in erysipelas.[100]

Eight studies did not present the results of lower-limb cellulitis separately. Of these, Rahmouni *et al.* examined the use of MRI in cellulitis[90] and Chao *et al.* utilized ultrasound imaging for soft-tissue infections in the paediatric population.[29] Bonnetblanc *et al.* investigated a modification of the LRINEC score,[26] two studies focused on multiple laboratory and clinical markers[98,99] and Radkevich *et al.* investigated coagulable factors.[87] Wang *et al.* discussed tissue oxygen saturation monitoring[107] and Ko *et al.* examined the use of thermal imaging cameras.[54,55]

Discussion

We found no robustly developed and validated diagnostic tools or criteria for lower-limb cellulitis. A variety of potential tools have been explored so far, including biochemical tests, imaging, predictive scoring and clinical features. However, in seven of the eight included studies, cellulitis was not the main pathology of interest and was used as a comparator. Three studies compared cellulitis with rare differential diagnoses, such as osteomyelitis, which provide limited clinical applicability. This diversity in the tools explored emphasizes the difficulty in making a correct diagnosis on first presentation.

All eight included studies identified in this review were observational studies.[16–19] The sample sizes were small, with only two studies including more than 100 patients with cellulitis.[16,18] No criteria or tools have been subsequently validated in a large prospective study.

Despite cellulitis being a common presentation in community settings, all the tools identified to date have been developed and tested in secondary care, with limited evidence of validity or applicability in community settings. No study stated that the gold standard reference for clinical diagnosis was a board certified dermatologist or other specialist with cellulitis expertise. Only one study clearly stated who made the cellulitis diagnosis.[17]

All the tools developed to date can be accessed by secondary care, are already available and, with the exception of CT imaging, are inexpensive. The severity of cellulitis is likely to be worse in secondary care. However, none of these tools can be used until they are validated in higher-quality studies.

Three studies included rare pathologies that provide very limited clinical relevance as they are not common misdiagnoses of cellulitis.[110] Blood tests need to be interpreted with caution, as ESR, CRP and WBC count are nondiscriminatory markers, but can be used to guide a clinician when the differential diagnoses have been narrowed. High levels of these markers can also help point towards rarer pathologies such as NF. Only one study included paediatric patients,[20] therefore findings cannot be applied to this under-researched population.

This is the first systematic review that aimed to identify diagnostic criteria or tools developed for lower-limb cellulitis. The key strength of this review is the comprehensive search strategy used, which was supported by an experienced information specialist. The focus of this review was lower-limb cellulitis and therefore, if the site of cellulitis was not specified or a study did not present the results of lower-limb cellulitis separately, then the study was excluded.

The limitations of this review stem from the number and quality of the studies included. Data could not be pooled as the index tests were not comparable. Also, 28 papers were excluded as the site of cellulitis was not specified or the results for lower-limb cellulitis were not separated. These papers did include diagnostic criteria or tools that need to be further evaluated. Owing to time constraints, only the first 100 results on Google Scholar were included.

In conclusion, this systematic review has identified an important research gap in the diagnosis of lower-limb

cellulitis. There is currently insufficient evidence available to support the validity of any diagnostic criteria or tools that have been developed for lower-limb cellulitis. As such, their utility for clinical practice or research remains unclear. Future studies should employ prospective designs, using diagnosis by board certified specialists with cellulitis expertise as the reference diagnostic standard and should be validated in both primary and secondary care settings. To gain a better understanding of what ought to be included in diagnostic criteria or tools, qualitative research that includes input from a range of healthcare professionals and patients with experience of managing lower-limb cellulitis should be carried out.

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