

Red flags presented in current low back pain guidelines: a review

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Abstract

Objective The purpose of this study was to identify and descriptively compare the red flags endorsed in guidelines for the detection of serious pathology in patients presenting with low back pain to primary care.

Method We searched databases, the World Wide Web and contacted experts aiming to find the multidisciplinary clinical guideline in low back pain in primary care, and selected the most recent one per country. We extracted data on the number and type of red flags for identifying patients with higher likelihood of serious pathology. Furthermore, we extracted data on whether or not accuracy data (sensitivity/specificity, predictive values, etc.) were presented to support the endorsement of specific red flags.

Results We found 21 discrete guidelines all published between 2000 and 2015. One guideline could not be retrieved and after selecting one guideline per country we included 16 guidelines in our analysis from 15 different countries and one for Europe as a whole. All guidelines focused on the management of patients with low back pain in a primary care or multidisciplinary care setting. Five guidelines presented red flags in general, i.e., not related to any specific disease. Overall, we found 46 discrete red flags related to the four main categories of serious pathology:

malignancy, fracture, cauda equina syndrome and infection. The majority of guidelines presented two red flags for fracture ('major or significant trauma' and 'use of steroids or immunosuppressors') and two for malignancy ('history of cancer' and 'unintentional weight loss'). Most often pain at night or at rest was also considered as a red flag for various underlying pathologies. Eight guidelines based their choice of red flags on consensus or previous guidelines; five did not provide any reference to support the choice of red flags, three guidelines presented a reference in general, and data on diagnostic accuracy was rarely provided.

Conclusion A wide variety of red flags was presented in guidelines for low back pain, with a lack of consensus between guidelines for which red flags to endorse. Evidence for the accuracy of recommended red flags was lacking.

Keywords Low back pain · Practice guidelines/clinical guidelines

Introduction

Low back pain remains a common condition among primary care patients with an estimated lifetime prevalence of 13.8 % for chronic pain and 80 % for any episode of pain [1–3]. European guidelines for the management of low back pain in primary care define low back pain as “pain and discomfort” localized below the costal margin and above the inferior gluteal folds, with or without leg pain. Nonspecific low back pain is commonly defined as low back pain without any known pathology [4]. Although nonspecific low back pain accounts for about 85–90 % of back pain [5–7], the remaining patients may have neurologic impairments (e.g., spinal stenosis, radiculopathy) or

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serious underlying diseases (e.g., malignancies, fractures), of which the latter necessitates timely and accurate diagnosis [6, 7].

Serious pathology in patients presenting with low back pain includes malignancy, spinal fractures, cauda equina syndrome (CES), infection or aortic aneurisms. Spinal malignancy and vertebral fracture are the most frequent serious pathologies of the spine [8]. However, the absolute magnitude of occurrence may be regarded as rare. Among patients with low back pain presenting in primary care less than 1 % will have spinal malignancy (primary vertebral tumor or vertebral metastasis) and about 4 % will have spinal fracture [5, 9]. CES or spinal infections are even rarer, with an estimated prevalence of 0.04 and 0.01 %, respectively, among patients with low back pain [5, 9]. The spine is the most common bony site for musculoskeletal tumors. The majority of spinal malignancies are the result of metastases of other tumors in the body, mainly from breast, lung or prostate cancer [10]. Vertebral compression fractures occur in almost 25 % of all postmenopausal women and the prevalence of compression fractures linearly increases with advancing age, up to 40 % in women 80 years of age [11].

Clinicians are advised by guidelines to evaluate serious underlying pathology by checking for red flags (or alarm signals) during the history taking and physical examination [12]. The presence of red flags may indicate underlying serious pathology in patients with low back pain. Current guidelines often present a list of red flags, which are considered to be associated with an increased risk of the presence of underlying serious pathology in the spine, often without consideration given to the diagnostic accuracy of the red flag (test). While most guidelines recommend screening for red flags, there is variation in which red flags are endorsed, and there exists heterogeneity in precise definitions of the red flags (e.g. ‘trauma’, ‘severe trauma’, ‘major trauma’). An overview of recommended red flags in the guidelines is lacking. The purpose of this study was to identify and compare the red flag recommendations in current guidelines for the detection of medically serious pathology in patients presenting with low back pain.

Method

Design

Overview of recommendations on red flag screening in low back pain guidelines.

Search strategy

We searched for clinical guidelines in primary health care concerning adults with low back pain (date of last search

January 30, 2016). Our starting point was a previously published review article including 15 national and international guidelines for diagnosis and treatment of low back pain [12]. First, we checked for updates of these 15 guidelines. Additionally, we searched for other clinical practice guidelines using electronic databases: Medline, PEDro (key words: low back pain, practice guidelines, clinical guidelines), National Guideline Clearinghouse (<http://www.guideline.gov>; key word: low back pain), and National Institute for Health and Clinical Excellence (<http://www.nice.org.uk>; key word: low back pain). Furthermore, we performed searches via Google, performed snowballing and citation tracking on publications found and consulted experts in the field. The search was aimed at finding all the clinical guidelines that exist. No language or date restriction was applied. We defined ‘guideline’ as: “... contains systematically developed statements including recommendations intended to optimize patient care and assist physicians and/or other health care practitioners and patients to make decisions about appropriate health care for low back pain under the auspices of a medical specialty association; relevant professional society; public or private organization” (according to the National Guideline Clearinghouse). When one country had more than one guideline, we selected the most recent multidisciplinary guideline.

Data extraction

We extracted data on the number and type of red flags for serious pathology for each guideline using a standardized form. For each red flag, we scored if the red flag was supported by the literature presenting its diagnostic accuracy (e.g., data on sensitivity/specificity, predictive values, etc.), if it was supported by consensus of the guideline committee only, or if no information was given to support the endorsement of red flags. One author (NP) extracted the data, which were checked by a second (APV). The data were summarized using tables.

Results

Search results

First, of the original 15 guidelines of previously published review article [12], we excluded the European guideline for chronic low back pain [13], given that red flags were presented in the European guideline for acute low back pain only [4]. Eight countries updated their guideline (Austria, Canada, Finland, Germany, Netherlands, Norway, Spain, and United States) [17–24]; of three countries, we found more than one updated guideline (Austria, Netherlands, and United States). We found two updated guidelines from

Austria including an update of a multidisciplinary guideline from 2007 and one specifically for radiologists [25] of which we selected the multidisciplinary one [17]. The updated guidelines from The Netherlands included a multidisciplinary guideline and one specifically for physiotherapists [26] of which we selected the multidisciplinary one [21]. The United States had two multidisciplinary guidelines [24, 27] and one specifically for physiotherapists [28] of which we selected for this overview the latest multidisciplinary guideline [24] linked to a website [29]. The guidelines of Finland and Norway were not available in English, so colleagues were contacted to extract the relevant data.

Next, we performed a broad search aiming to identify additional guidelines. In total, we identified 21 guidelines, of which four were excluded (see above) as we selected one guideline per country. We found three new guidelines (Philippines, Malaysia, and Mexico) of which one guideline (Mexico) [14] could not be retrieved [15, 16]. Finally, 16 discrete guidelines were included in this review (see Table 1).

Description of the guidelines

The guidelines were published between 2000 (France) and 2015 (Finland), with the publication date of one guideline unknown (Malaysia). The target population was mostly adults (>15 or 18 years) with low back pain. Nine guidelines used the term nonspecific low back pain, three guidelines also included people with radiculopathy, four guidelines specifically focused on patients with acute low back pain (defined as a duration less than 3 months), and one guideline included patients with acute and/or recurrent low back pain (New Zealand) (see Table 1).

Red flags

All guidelines recommended screening patients for suspected serious pathologies by using red flags. Eight guidelines presented red flags for various forms of serious underlying disease specifically (Australia, Finland, France, Germany, Italy, Netherlands, United Kingdom, USA) [19, 20, 24, 30–33]; one guideline combined red flags for malignancy and infection (Canada) [18]; two guidelines presented general red flags, but separately for cauda equina syndrome (Europe, New Zealand) [4, 34]; and five guidelines presented red flags without targeting a specific underlying pathology (Austria, Malaysia, Norway, Philippines, Spain) [15–17, 22, 23].

The pathologies most commonly referred to in the guidelines were: malignancy (9 guidelines); fracture (9 guidelines) of which one guideline focused on compression fractures only (Finland), and three guidelines

distinguished between traumatic and osteoporotic fractures (Canada, Netherlands, United States); infection (8 guidelines) of which one focused only on ankylosing spondylitis (Netherlands), two guidelines separately focused on infection and spondyloarthropathies (Italy, United States) and two on infection and ankylosis spondylitis (Canada, France); cauda equina syndrome (7 guidelines); aneurism (3 guidelines); myelopathy (United States) and severe spondylolisthesis (Netherlands). We found 46 different guideline endorsed red flags for malignancy, fractures, infection and cauda equina syndrome (see Table 2).

None of the guidelines provided a detailed definition of each red flag nor a precise description of when a red flag could be considered positive, e.g., when does a patient have ‘osteoporosis’ or ‘loading pain’. For the presentation, we clustered red flags when the wording suggested a comparable definition or description, e.g., some guidelines state as a red flag for a fracture the ‘use of steroids’ or ‘corticosteroid use’, while others add the prefix ‘systemic’, ‘chronic’ or ‘prolonged’. Others categorize corticosteroid use with ‘immunosuppressive use’.

Malignancy

There are a wide variety of recommended red flags for malignancy. In total, 14 red flags were specifically related to malignancy. Two red flags were mentioned in almost all guidelines: a ‘history of cancer’ was included in all guidelines, and ‘unexplained or unintentional weight loss’ was included in all but three guidelines (Spain, United Kingdom and United States). Almost all guidelines mentioned pain as a red flag, but the description of the kind of pain differed. Most often ‘pain at rest’ or ‘pain at night’ was considered as a red flag. Nine red flags for malignancy were mentioned in a single guideline only: ‘multiple cancer risk factors (unspecified)’ and ‘strong clinical suspicion’ (United States), ‘reduced appetite’ and ‘rapid fatigue’ (Germany), ‘elevated ESR’ and ‘general malaise’ (The Netherlands), ‘fever’, ‘paraparesis’ and ‘progressive symptoms’ (Finland). One guideline presents a combination of red flags for malignancy: ‘Patient over 50 (particularly over 65), with first episode of severe back pain and other risk factors for malignancy, such as history of cancer/carcinoma in the last 15 years, unexplained weight loss, failure of conservative care (4 weeks)’ (Canada), see Table 1.

Fracture

In total, 11 red flags were considered to be specifically related to fractures. All but one guideline (United

Table 1 Clinical guidelines regarding red flags

Guideline	Patient population	Red flags	Cited evidence to support inclusion
Australia [17] Clinicians and patients	Acute (<3 months) nonspecific low back pain	Fracture: History of (major) trauma Minor trauma (if >50 years, history of osteoporosis and taking corticosteroids) Malignancy: Past history of malignancy; age >50 years; failure to improve with treatment; unexplained weight loss; pain at multiple sites; pain at rest Infection: Symptoms and signs of infection (e.g. fever); risk factors for infection (e.g. underlying disease process, immunosuppression, penetrating wound); bone tenderness over the lumbar spinous process Aortic aneurism: Absence of aggravating features General: Age (<20, >55 years); increasing pain despite treatment; Trauma; history of cancer; osteoporosis; pain in rest; accompanying thoracic pain; pain increase in flexion; use of corticosteroids, immunosuppression use; drug abuse; HIV; neurological signs (neurological claudication); malaise; fever; unexplained weight loss; deformities Compression fracture: Severe onset of pain with minor trauma, age >50, prolonged steroid intake or structural deformity Fracture or infection: Significant trauma; use of intravenous drugs or steroids Malignancy: Patient over 50, but particularly over 65, with first episode of severe back pain and other risk factors for malignancy: history of cancer/carcinoma in the last 15 years, unexplained weight loss, failure of conservative care (4 weeks) Malignancy or infection: Severe unremitting (nonmechanical) worsening of pain (at night and pain when laying down); weight loss; fever; history of cancer/HIV; widespread neurological signs; Cauda equina syndrome: Sudden onset of new urinary retention, fecal incontinence, saddle (perineal) anaesthesia, radicular (leg) pain often bilateral, loss of voluntary rectal sphincter contraction Ankylosis spondylitis: Younger adults who, in the absence of injury, present with a history of needing to get out of bed at night and reduced side bending	Fracture: Scavione et al. [51, 52] Malignancy: Deyo and Diehl [41] Infection: Deyo et al. [9]
Austria [30] Professionals of various disciplines	Nonspecific low back pain		Royal College of General Practitioners [53]
Canada [18] Primary health care providers	Nonspecific low back pain with/without sciatica/radiculopathy		Based on previous guidelines: USA (2008); Europe [4]; Canada (2005); Australia [17] and consensus

Table 1 continued

Guideline	Patient population	Red flags	Cited evidence to support inclusion
Europe COST-13 [4] Patients, health care providers, guideline developers	Acute (<3 months) nonspecific low back pain	<p>General:</p> <p>Age of onset less than 20 years or more than 55 years; recent history of violent trauma; constant progressive, nonmechanical pain (no relief with bed rest); thoracic pain; past medical history of malignant tumor; prolonged use of corticosteroids; drug abuse, immunosuppression, HIV; systemically unwell; unexplained weight loss; widespread neurological symptoms (including cauda equina syndrome); structural deformity; fever</p> <p>Cauda equina syndrome:</p> <p>Likely to be present when patients describe bladder dysfunction (usually urinary retention, occasionally overflow incontinence), sphincter disturbance, saddle anesthesia, global or progressive weakness in the lower limbs, or gait disturbance</p>	Royal College of General Practitioners [53] Malignancy (history (of cancer) and high ESR): van den Hoogen et al. [54]
Finland [19] Professionals of various disciplines	Adult (>15 years) low back pain patients	<p>Compression fracture:</p> <p>Age over 50 years, fall, use of glucocorticoids, osteoporosis</p> <p>Malignancy:</p> <p>Anamnestic cancer, weight loss without obvious reason, fever, progressing symptoms, night pain, pain over one month, paraparesis</p> <p>Bacterial spondylitis/spondylodiscitis:</p> <p>Previous back surgery; urinary tract or skin infection; immunosuppression; intravenous drug use</p> <p>Cauda equina syndrome:</p> <p>Urinary retention and anal sphincter insufficiency, saddle region anesthesia, paresthesia and paresis symptoms in the lower extremities</p> <p>Aneurism:</p> <p>Instant, unbearable pain; age over 50 years; disorder in hemodynamics</p>	Based on Europe guideline [4]
France [31] General practitioner; Rheumatologist; Orthopedic	Acute LBP (<3 months) with/without sciatica	<p>Fracture:</p> <p>Occurrence of trauma; Corticosteroids use; Age over 70</p> <p>Malignancy:</p> <p>Age over 50, unexplained weight loss, history of tumor or failure of symptomatic treatment</p> <p>Infection:</p> <p>Fever, pain with recrudescence at night, patient undergoing immunosuppressant therapy, urinary tract infection, IV drug use, prolonged corticosteroid therapy</p> <p>Ankylosing spondylitis</p> <p>Pain which awakened the subject at night and made him leave the bed, pain not relieved by lying down but improved by exercise, 3 months duration of the complaints, morning stiffness lasting >30 min, reduced lateral mobility, flexion (<20°) or extension (<40°) of the lumbar spine</p> <p>Cauda equina syndrome:</p> <p>Sciatica, saddle anesthesia, sphincter problems, incontinence</p>	<p>Malignancy: Deyo et al. [41]</p> <p>Ankylosing spondylitis: Gran [55]</p>

Table 1 continued

Guideline	Patient population	Red flags	Cited evidence to support inclusion
Germany [20] Physicians and nonmedical health care professionals	Nonspecific low back pain	Fracture: Serious trauma (e.g. through a car accident, fall from a great height, sports accident); minor trauma (e.g. coughing, sneezing, heavy lifting in elderly, potential osteoporosis patients); systemic steroid therapy Malignancy: Old age; history of malignancies; general symptoms: loss of weight, reduced appetite, rapid fatigue; pain, increasing in supine position; intense nocturnal pain Infection: General symptoms such as recent fever, chills, reduced appetite, rapid fatigue; previous bacterial infections; intravenous drug abuse; immunosuppression; consuming underlying diseases; very recent spinal infiltration treatment; intense nocturnal pain Fracture: Elderly age; female gender; loading pain; significant trauma; osteoporosis; chronically use of steroids; previous fractures Malignancy: Age over 50; history of cancer; loss of weight; no improvement after 4–6 weeks; continuous pain or worsening pain, pain at rest and during the night pain Infection” Fever; infection history; drug addiction; HIV; immunosuppressive therapy; night and rest pain Cauda equina: Urinary retention; saddle anesthesia; anal sphincter reduced tonus; both legs pain; spread sensory deficit Aneurism: Age >60; atherosclerosis; abdominal pulsing mass; night and rest pain; sciatica Inflammatory low back pain/spondylarthropaties: Age <45 years; pain at night/morning; NSAID sensibility; improvement with movement; insidious onset; rigidity duration >3 months; history of enthesitis/mono-oligo arthritis; acute uveitis; family history of spondyloarthritis; ulcerating colitis; Crohn’s disease; psoriasis	Consensus by clinicians and European guidelines [4]
Italy [32] Primary care and secondary care	Nonspecific low back pain and sciatica		Not referenced
Malaysia [16]	Low back pain	General Onset of pain at age <20 years or >55 years; history of trauma, cancer and osteoporosis; significant weight loss; use of systemic steroids; drug or alcohol abuse; HIV; infection; thoracic pain; unremitting night pain or pain at rest; fever for 48 h; sudden onset or unexplained changes in bowel or bladder control; sudden onset or otherwise unexplained bilateral leg weakness, or progressive motor weakness in the leg with gait disturbance; saddle numbness or anesthesia; severe restriction of lumbar flexion; structural spinal deformity	Based on: Waddell [56]

Table 1 continued

Guideline	Patient population	Red flags	Cited evidence to support inclusion
The Netherlands [21] Various health care providers	Nonspecific low back pain	Vertebral fracture: Severe low back pain after trauma Osteoporotic vertebral fracture: Onset of LBP after the age of 60, female gender, low body weight, prolonged corticosteroid use, increased thoracic kyphosis Malignancy: Onset of the low back pain after age 50 years, continuous pain regardless of posture or movement, nocturnal pain, general malaise, history of malignancy, unexplained weight loss, elevated erythrocyte sedimentation rate (ESR) Ankylosing spondylitis: Onset of low back pain before age 20 years, male sex, iridocyclitis, history of unexplained peripheral arthritis or inflammatory bowel disease, pain mostly nocturnal, morning stiffness >1 h, less pain when moving, positive reaction on painkillers (NSAIDs), elevated erythrocyte sedimentation rate (ESR) Severe spondylololsthesis: Onset of low back pain before age 20 years, palpable misalignment of the processi spinosi at the L4–L5 level	Not specifically referenced, only generic references
New Zealand [34] Physical therapy; general practitioner; osteopath Multidisciplinary	Acute (<3 months) low back pain and recurrent episodes	General: Unremitting night pain, pain worse when lying down; Significant trauma; weight loss, history of cancer, fever; use of intravenous drugs or steroids; patient over 50 years old Cauda equina syndrome: Urinary retention, fecal incontinence, widespread neurological symptoms and signs in the lower limb, including gait abnormality, saddle area numbness and a lax anal sphincter	Not referenced
Norway [22] Doctors, physiotherapist or chiropractors	Low back pain with/without nerve root affection	General: Age under 20 or above 55 years; constant pain, possibly increasing over time; pain whilst at rest; general feeling of illness and/or loss of weight. Injury or trauma, cancer, use of steroids or immunosuppressant, drug abuse in history; widespread neurological signs. Deformity of the spine. Declared morning stiffness that lasts for more than 1 h. High ESR	Based on European guidelines [4]
Philippine [15] Physiatrists [Rehabilitation Medicine Specialist's (Physiatrists)]	Nonspecific low back pain	General: Age under 20 or over 55 of age; violent trauma; constant, progressive, nonmechanical pain; thoracic or abdominal pain; pain at night that is not eased by a prone position; history of or suspected cancer, HIV or other pathologies that can cause back pain; chronic corticosteroid consumption; unexplained weight loss, chills or fever; significant limitation of lumbar flexion; loss of feeling in the perineum; Recent onset of urinary incontinence	Based on previous guidelines: Italy [32]; UK [33]; Canada (2007); USA (2012) [27]; Chou et al. [6]; Chou et al. [38]
Spain [23] Primary care; physiotherapy Monodisciplinary	Nonspecific low back pain	General: Pain <20 or >50 age; thoracic spine pain; deficit neurologic; deformity, not flexion of 5th; bad general state, fever; trauma or neoplasms; use of corticosteroids; addictions; immunodeficiency, AIDS	Based on: European guideline (COST B13 working group) [3]

Table 1 continued

Guideline	Patient population	Red flags	Cited evidence to support inclusion
United Kingdom (NCC-PC/ NICE) [33] General practitioners and patients	Nonspecific low back pain	<p>Fracture: Osteoporotic fractures typically affect older people (women more than men) and those with other chronic illnesses; particularly if they have used long-term oral steroids</p> <p>Malignancy: Malignancy is more common in older people and those with a past history of tumors known to metastasize to bone</p> <p>Infection: Infection should be considered in those who may have an impaired immune system, e.g. people living with HIV, or who are systemically unwell</p> <p>Pain that continues for longer than 6 weeks or who further deteriorate between 6 weeks and 1 year, the possibility of a specific cause needs to be re-considered</p>	Not referenced
United States [24] Primary care providers Multidisciplinary	Nonspecific low back pain	<p>Fractures: Major trauma</p> <p>Osteoporotic fractures: Osteoporosis, osteoporosis risk (unspecified)</p> <p>Malignancy: History of cancer, multiple cancer risk factors (unspecified), strong clinical suspicion</p> <p>Cauda equina syndrome (CES): New bowel or bladder dysfunction, perineal numbness or saddle anesthesia, persistent/increasing lower motor neuron weakness</p> <p>Infection: Immunocompromised status, urinary tract infection, intravenous drug use, fever/chills with rest or night pain</p> <p>Myelopathy: New-onset Babinski or sustained clonus, new-onset gait or balance abnormalities, upper motor neuron weakness</p> <p>Spondylarthropathies: Ankylosing spondylitis at least 4 of the following: age of pain onset <40 years; insidious onset; improvement with exercise; no improvement with rest; pain at night (with improvement upon rising); morning stiffness</p> <p>Reactive arthritis/reiter's syndrome recent history of genitourinary or gastrointestinal tract infection; acute onset; asymmetrically painful and swollen joints; weight loss; high temperatures</p> <p>Spondyloarthropathy associated with inflammatory bowel disease (IBD) abrupt onset; asymmetric, affecting lower limbs; generally subsides in 6–8 weeks; other symptoms: uveitis, chronic skin lesions, dactylitis, enthesitis</p> <p>Psoriatic arthritis: asymmetric, affecting distal joints; morning stiffness; pain accentuated by prolonged immobility, alleviated by physical activity; psoriatic lesions</p>	Based on previous guidelines: European guideline (COST B13 working group) [4]; NICE [33]; Koes et al. [12]; Institute for Clinical Systems Improvement (ICSI) [27]; Malignancy: Chou et al. [50] Ankylosing spondylitis: Yu et al. [57]; Rajesh and Brent [58]

Table 2 Red flags endorsed for specific disease

Condition	Red flag	Endorsed by guideline	
Malignancy	History of malignancies/cancer	Australia, Canada, Finland, France, Germany, Italy, Netherlands, United Kingdom, United States	
	(Unexplained/unintentional) Weight loss	Australia, Canada, Finland, France, Germany, Italy, Netherlands	
	Pain		
	(Increasing) Pain at night	Finland, Germany, Italy, Netherlands	
	(Continuous) Pain at rest	Australia, Italy, Netherlands	
	At multiple sites	Australia	
	Over 1 month (duration)	Finland	
	Pain at night that is not eased by a prone position (or increasing in supine position)	Germany	
	Failure to improve with treatment (>4–6 weeks)	Australia, Canada, France, Italy	
	Age		
	Age over 50 years	Australia, France, Italy, Netherlands	
	Old age	Germany, United Kingdom	
	Elevated erythrocyte sedimentation (ESR)	Netherlands	
	General malaise	Netherlands	
	Multiple cancer risk factors	United States	
	Strong clinical suspicion	United States	
	Reduced appetite	Germany	
	Rapid fatigue	Germany	
	Progressive symptoms	Finland	
	Fever	Finland	
	Paraparesis	Finland	
	Age over 50 (over 65), first episode of severe back pain [and history of cancer/carcinoma in the last 15 years, unexplained weight loss, failure of conservative care (4 weeks)]	Canada	
	Fracture	(History of) Major/significant trauma	Australia, Canada, Finland, France, Germany, Italy, Netherlands, United States
		(Systemic) Use of steroids	Canada, Finland, France, Germany, Italy, Netherlands, United Kingdom
		Osteoporosis	Finland, Italy, United States
		Female gender	Italy, Netherlands, United Kingdom
		Age	
Age >50		Canada, Finland	
Age >60		Netherlands	
Older age (over 70)		France, Italy, United Kingdom	
Pain			
Sudden onset		Canada	
Loading pain		Italy	
Minor trauma		Germany	
Fracture in history/previous fractures		Italy	
Low body weight		Netherlands	
Increased thoracic kyphosis		Netherlands	
Structural deformity		Canada	
Minor trauma (if age >50, history of osteoporosis and taking corticosteroids)		Australia	
Severe onset of pain (with minor trauma, age >50, prolonged steroid intake or structural deformity)		Canada	

Table 2 continued

Condition	Red flag	Endorsed by guideline	
Infection	Fever ≥ 38 °C	Australia, France, Germany, Italy, United States	
	Use of corticosteroids or immunosuppressant therapy	Australia, Finland, France, Germany, Italy, United States	
	Intravenous drug abuse/drug addiction	Finland, France, Germany, Italy, United States	
	Immunodeficiency/AIDS	Italy, United Kingdom	
	Urinary tract infection	Finland, France, United States	
	Pain	Pain with recrudescence at night	France
		Intense night pain (and rest pain)	Germany, Italy, United States
		Bone tenderness over the lumbar spinous process	Australia
		Previous back surgery	Finland, Germany
		Previous bacterial infections	Germany, Italy
		Penetrating wound	Australia
		Reduced appetite	Germany
	Cauda equina syndrome (CES)	Rapid fatigue	Germany
		Impaired immune system	United Kingdom
		Underlying disease process	Australia
		Saddle anesthesia/perineal numbness	Canada, Europe, Finland, France, Italy, New Zealand, United States
		(Sudden onset) Bladder dysfunction (e.g. urinary retention, overflow incontinence)	Canada, Europe, Finland, France, Italy, New Zealand, United States
Sphincter disturbance/reduced tonus		Canada, Europe, Finland, France, Italy, New Zealand	
Progressive weakness in lower limbs/lower motor neuron weakness		Europe, Finland, United States	
(Wide) Spread sensory deficit (in lower limbs)	Italy, New Zealand		
Gait disturbance/abnormality	Europe, New Zealand		
Fecal incontinence	Canada, New Zealand		
Pain (radiating) in both legs	Canada, Italy		
Sciatica	France		

Kingdom) mentioned ‘major or significant trauma’ as a red flag, and ‘use of steroids or immunosuppressors’ was mentioned as a red flag in nine guidelines. Seven guidelines mentioned ‘older age’ as a red flag, but the cut-off varied between 50 and over 70 years. Five red flags for fracture were mentioned in a single guideline only: ‘previous fractures’ (Italy), ‘low body weight’ and ‘increased thoracic kyphosis’ (The Netherlands), ‘structural deformity’ (Canada) and ‘minor trauma’ (Germany). Three guidelines mentioned female gender as a red flag specifically for osteoporotic/compression fractures (Italy, Netherlands, and United Kingdom). Two guidelines presented a combination of red flags to be related to (compression) fractures: ‘minor trauma if age is over 50 and there is a history of osteoporosis and corticosteroid use’ (Australia) or ‘severe onset of pain with minor trauma, age >50, prolonged steroid intake or structural deformity (for compression fracture)’ (Canada).

Infection

Overall, 13 red flags were recommended in relation to infection. The most frequently mentioned red flags were: fever (12 guidelines), use of corticosteroids or immunosuppressant therapy (10 guidelines) and intravenous drug abuse (11 guidelines). Five guidelines mentioned pain as red flag: ‘pain worse at night’ (France); ‘intense nocturnal pain’ (Germany); ‘night and rest pain’ (Italy); ‘fever/chills in addition to pain with rest or at night’ (United States) or ‘bone tenderness over the lumbar spinous process’ (Australia).

Cauda equina syndrome

Nine red flags were recommended in relation to cauda equina syndrome (CES), of which two were frequently mentioned: ‘saddle anesthesia (perineal numbness)’ and

Table 3 Red flags endorsed unrelated to specific disease

Red flag	Endorsed by guideline
Pain	
Onset of pain <20 or >50 years old	Austria, Europe, Malaysia, Norway, Philippine, Spain
Constant, progressive, nonmechanical pain	Canada, Europe, Philippine
No pain relief with bed rest	Europe
Thoracic (or abdominal) pain	Austria, Europe, Malaysia, Philippine, Spain
(Continuous) Pain at rest ^a	Austria, Canada, Malaysia, New Zealand, Norway
(Increasing) Pain at night ^{a,c}	Canada, Malaysia, New Zealand
Pain increase in flexion	Austria
Increasing pain despite treatment	Austria
Pain at night that is not eased by a prone position (or increasing in supine position) ^a	Philippine
History of malignancies/cancer ^a	Austria, Canada, Europe, Malaysia, New Zealand, Norway, Philippine, Spain
(Unexplained/unintentional) Weight loss ^a	Austria, Canada, Europe, Malaysia, New Zealand, Norway, Philippine
Fever ≥ 38 °C ^{a,c}	Austria, Canada, Europe, Malaysia, New Zealand, Philippine, Spain
General malaise ^a	Austria, Norway, Spain
Elevated erythrocyte sedimentation (ESR) ^a	Norway
Age over 50 years ^a	New Zealand
(History of) Major/significant trauma ^b	Austria, Europe, Malaysia, New Zealand, Norway, Philippine, Spain
(Structural spinal) deformity ^b	Austria, Europe, Malaysia, Norway, Spain
(Systemic) Use of steroids ^b	Malaysia, New Zealand,
Osteoporosis ^b	Austria, Malaysia
Intravenous drug abuse/drug addiction ^c	Austria, Europe, Malaysia, New Zealand, Norway, Spain
Use of corticosteroids or immunosuppressant therapy ^c	Austria, Europe, Norway, Philippine, Spain
Immunodeficiency/HIV/AIDS ^c	Austria, Europe, Malaysia, Philippine, Spain
Saddle anesthesia/perineal numbness ^d	Malaysia, Philippine
(Sudden onset) Bladder dysfunction (e.g. urinary retention, overflow incontinence) ^d	Malaysia, Philippine
(Wide) Spread sensory deficit (in lower limbs) ^d	Austria, Canada, Europe, Norway, Spain
Progressive weakness in lower limbs/lower motor neuron weakness ^d	Malaysia
Gait disturbance/abnormality ^d	Malaysia
Progressive weakness in lower limbs/lower motor neuron weakness ^d	Malaysia
Significant limitation of lumbar flexion	Malaysia, Philippine
Not flexion of 5th lumbar spine	Spain
Morning stiffness	Norway

^a Endorsed elsewhere for malignancy, ^b endorsed elsewhere for fracture, ^c endorsed elsewhere for infection, ^d endorsed elsewhere for CES

‘(sudden onset of) bladder dysfunction’, both in nine guidelines. Only one red flag (‘sciatica’) is endorsed by one guideline (France).

Red flags unrelated to specific disease

Seven guidelines presented 23 red flags unrelated to a specific disease (Austria, Europe, New Zealand, Norway,

Philippine, Spain, Malaysia). Of these red flags, some were endorsed for a specific disease by other guidelines; 9 were endorsed for malignancy, 4 for fracture, 3 for infection and 6 for CES. In total, three unique red flags were presented and 6 unique pain items of which ‘pain under 20 or over 50 years’ and ‘thoracic pain’ were the most presented in 6 and 5 guidelines, respectively, see Table 3.

Level of evidence of red flags in the guidelines

Nine guidelines (Austria, Canada, Europe, Finland, Germany, Norway, Philippine, Spain, United States) based their recommendations for red flags on previous guidelines, of which two also included additional references (Europe, United States) and one explicitly stated that there was a consensus procedure (Germany), see Table 1. Four guidelines did not present any reference supporting their choice of red flags (Italy, Netherlands, New Zealand, United Kingdom); two guidelines presented references to support the choice of red flags (Australia, Malaysia), see Table 1. One guideline (France) presented diagnostic accuracy data (sensitivities and specificities) for the individual red flags. In the short version of the French guideline they only presented these data for two red flags for malignancy ('history of malignancy', 'unexplained weight loss'), while in their full paper all published accuracy data for red flags for malignancy and ankylosing spondylitis were presented.

Discussion

Main findings

We included 16 discrete guidelines for the management of patients with low back pain in the primary care setting presenting 46 different red flags for the four main categories of serious underlying pathologies (malignancy, fracture, infection and CES). Five guidelines endorsed red flags without targeting a specific pathology. Overall almost all guidelines endorsed two red flags for malignancy ('history of cancer' and 'unintentional weight loss') and two for fracture ('major or significant trauma' and 'use of steroids or immunosuppressors'). Red flags such as 'pain at night' or 'at rest' were recommended for various underlying pathologies. Existing accuracy data supporting the choice and endorsement of red flags was rarely used in the selected guidelines.

Comparison with the literature

Our findings that most guidelines vary in terms of the red flags endorsed, and contain little information on the diagnostic accuracy of the red flags, are in line with previous studies [12, 35, 36]. Although all guidelines present red flags and recommend their use to screen for serious pathology, only a few provide evidence of their accuracy. The American Pain Society presented an 'Evidence review' on the clinical evaluation and management of low back pain with a date of last search in July 2008 [37]. This report presents a clear overview of the known diagnostic accuracy of red flags for the detection of pathology

including malignancy, fracture, infection and CES. Several guidelines have been developed or updated since [27, 38], but without presenting the level of evidence to endorse red flags as cited in the evidence report (or refer to it). For example, the United States guideline (2014) endorses a greater number of red flags, but seldom underpins their recommendations with evidence.

Change in evidence is one of the reasons for updating guidelines [39]. New evidence can prompt the update of a guideline, but our review suggests that evidence related to screening for serious pathology has not prompted update of the guidelines studied. One exception is the United States physiotherapy guideline (excluded as it was not multidisciplinary), which presents a comprehensive table with red flags and their accompanying diagnostic accuracy data were available [28].

A recent paper summarizing two Cochrane diagnostic systematic reviews found nine studies evaluating the diagnostic accuracy of in total 29 red flags for fracture and 24 for malignancy [8]. There were differences in the red flags that demonstrated diagnostic utility and those endorsed by guidelines. It makes sense that red flags that do not show acceptable diagnostic accuracy are not endorsed in guidelines. Nevertheless, most red flags endorsed by the guidelines have never been evaluated for their diagnostic accuracy; 8 out of 14 red flags for malignancy and 6 of the 11 red flags for fracture.

For malignancy, the systematic review concluded that only 'history of cancer' is based on acceptable validity; it increases the probability of having cancer from 0.7 % (pre-test) to 33 % (95 % CI 22–46 %) [8]. Nevertheless, this conclusion is based on one study set in primary care and another in an emergency department where 36 % of patients were referred to because of a significant trauma [40, 41]. It is argued that 'history of cancer' is not very useful as a red flag, as it does not consider the type of primary cancer or the time since diagnosis [42]. For example, a history of recent (less than 5 years) breast cancer might be a more useful red flag than a history of leukemia greater than 20 years ago.

According to the systematic review, the red flags 'severe trauma', 'use of corticosteroids', 'older age' and 'presence of a contusion or abrasion' each increased the probability of a fracture from 4 % (pre-test) to between 9 and 62 % [8]. Three of these red flags were most often mentioned in the guidelines, but one ('presence of a contusion or abrasion') was absent from all guidelines.

An Australian population-based prospective cohort study of 1172 consecutive patients presenting to primary care for low back pain calculated the increased probability of fracture when a combination of red flags were positive [43]. When any three of the red flags 'female', 'age >70', 'severe trauma', and 'prolonged use of corticosteroids'

were present, the probability of fracture increased from 4 % (pre-test) to 90 % (95 % CI 34–99 %). Combining red flags to inform clinical decision-making remains largely unexplored in the literature. In addition, external validation of red flags used in combination to raise suspicion of disease is even more rare.

The European guideline reports explicitly “If any of these are present, further investigation (according to the suspected underlying pathology) may be required to exclude a serious underlying condition, e.g., infection, inflammatory rheumatic disease or cancer” [4]. Later in their guideline, the advice is diluted: “Individual ‘red flags’ do not necessarily link to specific pathology but indicate a higher probability of a serious underlying condition that may require further investigation. Multiple ‘red flags’ need further investigation.” Nevertheless, the majority of guidelines inferred that the presence of a red flag was absolute by recommending further diagnostic workup (e.g., advanced imaging). Given that up to 80 % of patients presenting to primary care may have at least one positive red flag [43], when combined with weak evidence in support of many red flags, this advice may cause harm to many patients through unnecessary imaging (increased radiation and health care costs), unnecessary alarming the patients (resulting in reduction of quality of life) and unnecessary treatment (including unnecessary surgery) [42, 44].

Strengths and weaknesses

For this overview, we searched for clinical guidelines. This required a broad and sensitive search of electronic databases, the World Wide Web and personal communication with experts in the field as most often clinical guidelines are made by (a combination of) professional bodies and published on national websites in their native languages. Not all guidelines have been translated into English, so it is possible that some non-English guidelines have been missed. Notwithstanding, we believe this would not have significantly influenced our conclusions. Furthermore, we selected a multidisciplinary guideline when more than one guideline per country was available. This resulted in an a priori selection of guidelines that might have influenced our conclusions. For instance, the United States physiotherapy guideline endorsed another set of red flags with accompanying diagnostic accuracy data where available, compared to the included multidisciplinary guideline [24, 28]. Hence, we have clustered red flags based on their assumed definition or description. Lack of standardization was evident when defining or describing red flags. For example, red flags related to nocturnal pain comprised ‘increasing pain at night’, ‘intense night pain’, ‘unbearable night and rest pain’, ‘pain at night not eased by prone

laying’ or ‘pain with recrudescence at night’. Similarly, there was a range of age cut-off for suspicion of fracture (>50, >60, >70, and ‘older age’). This lack of standardization may introduce confusion for the clinician, reduce the ability to describe red flags, and decrease the accuracy of any pooled results. Nevertheless, we do not think this clustering has influenced our conclusions.

Future directions

We found a wide variety of red flags, a lack of standardized description, and an overall lack of (presentation of their) diagnostic accuracy supporting their use. This highlights the need for a (limited) core set of red flags, ideally underpinned with acceptable diagnostic accuracy and endorsed by all guidelines. Next, the conduct of high quality diagnostic accuracy studies with clear operational definitions for each red flag should be commenced to assess the validity of these red flags individually or in combination (diagnostic model). Furthermore, guidance for primary care clinicians on how to ask for red flags needs attention, as there appeared little consensus between physiotherapists in a small qualitative study [45]. Given that the risk of serious disease for patients who present to primary care with low back pain is already low (e.g., infection <0.1 %, cancer about 0.7 %), red flags are of limited use when ruling out pathology. This is in contrast to other diagnostic models such as the Ottawa ankle rule where a negative test result may decrease the probability of ankle fracture from about 15 % to less than 2 % [46–48]. Therefore, diagnostic models that demonstrate an increased ability to detect serious disease should be explored. Some diagnostic models of red flags for fracture have been developed to identify patients with a greater risk of a fracture (up to 90 %), but they are yet to be validated [43, 49].

Conclusion

A wide variety of red flags is presented in the various guidelines for low back pain. Most guidelines based their recommendations for red flags on consensus; hardly any guidelines presented the evidence for endorsing red flags.

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Compliance with ethical standards

Conflict of interest All authors declare that there is no conflict of interest.

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