

# Prevalence and severity of pain in adult end-stage renal disease patients on chronic intermittent hemodialysis: a systematic review

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**Objectives:** Understanding the epidemiology of pain in patients on hemodialysis (HD) is crucial for further improvement in managing pain. The aim of this study was to systematically review available evidence on the prevalence and severity of pain in adult end-stage renal disease patients on chronic intermittent HD.

**Materials and methods:** We carried out a systematic review of the literature and developed a comprehensive search strategy based on search terms on pain and HD. We searched the databases MEDLINE, Scopus, PsycINFO, and CINAHL from the earliest date of each database to July 24, 2014. Manuscripts in all languages were taken into consideration. Two authors performed each step independently, and all disagreements were resolved after discussion with the third author. The quality of studies was estimated using the STROBE checklist and Cochrane risk-of-bias tool.

**Results:** We included 52 studies with 6,917 participants. The prevalence of acute and chronic pain in HD patients was up to 82% and 92%, respectively. A considerable number of patients suffered from severe pain. Various locations and causes of pain were described, with most of the studies reporting pain in general, pain related to arteriovenous access, headache, and musculoskeletal pain.

**Conclusion:** The findings of this systematic review indicate high prevalence of pain in HD patients and considerable gaps and limitations in the available evidence. Pain in this population should be recognized as a considerable health concern, and the nephrology community should promote pain management in HD patients as a clinical and research priority to improve patients' quality of life and pain-related disability.

**Keywords:** pain, hemodialysis, prevalence, intensity, epidemiology

## Introduction

The prevalence of chronic kidney disease is increasing worldwide, and is expected to continue increasing.<sup>1</sup> There are five stages of chronic kidney disease, with end-stage renal disease (ESRD) its final stage. With worsening of their kidney disease, patients develop many complications associated with a high risk of comorbidities and mortality.<sup>2-4</sup> Therefore, health care professionals caring for ESRD patients should aim not only to extend patients' life span but also improve their quality of life.<sup>5</sup> ESRD patients of all ages also have poor quality of life.<sup>6-8</sup> One of the most important qualitative parameters for evaluating patients' quality of life is bodily pain.<sup>9</sup> Therefore, it is important to understand and relieve bodily pain in this population, in order to improve their quality of life and quality of care.

ESRD is defined as loss of renal function requiring renal replacement therapy with any form of chronic dialysis or transplantation or occasionally conservative

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management in the elderly or those with significant comorbidities.<sup>10–12</sup> Incidentally, acute kidney injury requiring dialysis is not considered ESRD unless renal function fails to recover.<sup>13</sup>

Pain is common in ESRD patients.<sup>14</sup> Based on data from surveys, when asked, up to 50%–60% of dialysis patients admit to feeling pain, often very severe and not effectively managed, although many will not mention this to their doctors at clinic visits.<sup>14,15</sup> Pain is the major cause of depression, disturbed sleep patterns, impaired dialysis adequacy (if unable to endure full sessions), and likeliness of withdrawal from dialysis.<sup>16</sup>

Therefore, the objectives of this systematic review were to provide an updated analysis of epidemiological studies on pain in patients on hemodialysis (HD), to use both systematic and narrative methods to provide an objective summary of the literature, to assess study quality, and to provide recommendations for practice and research. Understanding the epidemiology of pain in patients on HD is crucial for further improvements in managing pain.

## Materials and methods

A systematic review of literature was carried out in accordance with the guidelines of the Center for Reviews and Dissemination<sup>17</sup> and the MOOSE study.<sup>18</sup> A priori protocol of the systematic review was designed and registered in the PROSPERO database (registration number CRD42015024894).

## Inclusion/exclusion criteria

We included all studies that reported epidemiology of pain in HD patients. Case reports and interventional studies reporting the effectiveness of interventions for the treatment of pain, as well as studies concerning peritoneal dialysis patients, continuous dialysis procedures, any other non-HD renal replacement therapy (eg, renal transplantation), plasmapheresis, children as participants and psychological studies concerning HD pain, were not included.

## Search strategy and record screening

The databases MEDLINE, Scopus, PsycINFO, and CINAHL were searched from the earliest date of each database to July 24, 2014, with the help of a library information specialist. The complex search strategy was initially designed for MEDLINE (Table 1), and was then thoroughly adapted for each database. There were no publication type limits. Studies in any language were considered. The search results were exported to the EndNote X7.4 program (Thomson Reuters,

**Table 1** MEDLINE search strategy

- 1) (h?emodialy\$ or h?emo\$filtrat\$ or ultrafiltrat\$).tw
- 2) exp Renal Dialysis/or exp Hemofiltration/or exp Hemodiafiltration/ or exp Ultrafiltration
- 3) 1 or 2
- 4) (pain\$ or dolo?r or hurt\$ or ache or aching or pang? or \$algia or \$dynia or discomfort or nocicept\$ or analge\$ or an?esthe\$ or pain?kill\$ or antihyperalg\$ or algesi\$ or anguish\$ or suffer\$).tw
- 5) exp Pain/ or exp Nociception/ or exp Analgesia/ or exp Anesthesia/ or exp Anesthetics/ or exp Analgesics/ or exp Stress, Psychological/ or exp Stress, Physiological/
- 6) 4 or 5
- 7) 3 and 6

New York, NY, USA), and duplicates were removed. Titles and abstracts of records retrieved by bibliographic search were initially screened by two authors (TB and EB) independently. Disagreements were resolved by the third author (LP). Once agreement was reached, the full text of each potentially eligible study was retrieved and analyzed by two authors independently. References and citations of included studies were downloaded from the Web of Science and screened by two authors independently (TB and EB) to identify additional citations that may have been missed through electronic database-search methods.

## Data extraction

A data-extraction form was designed specifically for the study, and piloted and applied to all patients treated with HD without separation of individual subgroups. The following data were extracted: type of study, manuscript language, country, number of patients, age, sex, and race/ethnicity of patients, time of HD, type of pain studied, time recall for pain assessment, prevalence of pain, causes of pain, pain-intensity measuring tool, and pain-intensity results.

## Assessment of study quality

STROBE checklist was used<sup>19</sup> for assessing the quality of observational studies, where each of the 22 points of the STROBE criteria was assigned equal weight, and a total score was calculated. The Cochrane risk-of-bias tool was used<sup>20</sup> for randomized controlled trials.

## Results

### Search results

The database search yielded a total of 16,057 (MEDLINE 8,907, Scopus 6,639, CINAHL 425, PsycINFO 86) records. Based on the screening, the authors assessed that 63 full-text studies could contain relevant data. Analysis of full texts indicated

that a total of 52 studies met our a priori inclusion criteria and were included in this review (Figure 1). Characteristics of included studies are presented in Table 2. The aim of the current review was to summarize epidemiological findings, and thus the summary of data using meta-analysis was not conducted. The findings were synthesized and described systematically.

## Excluded studies

Eleven studies were excluded for various reasons: reporting headache and cramps as number and percentage of sessions with the clinical event without specifying number of affected patients;<sup>21</sup> reporting prevalence of various handicaps of HD patients, but no information about pain prevalence;<sup>22</sup> not presenting results separately for patients on different types of dialysis;<sup>23</sup> seven were interventional studies with no data on baseline prevalence of pain;<sup>24–30</sup> and one was a case report.<sup>31</sup>

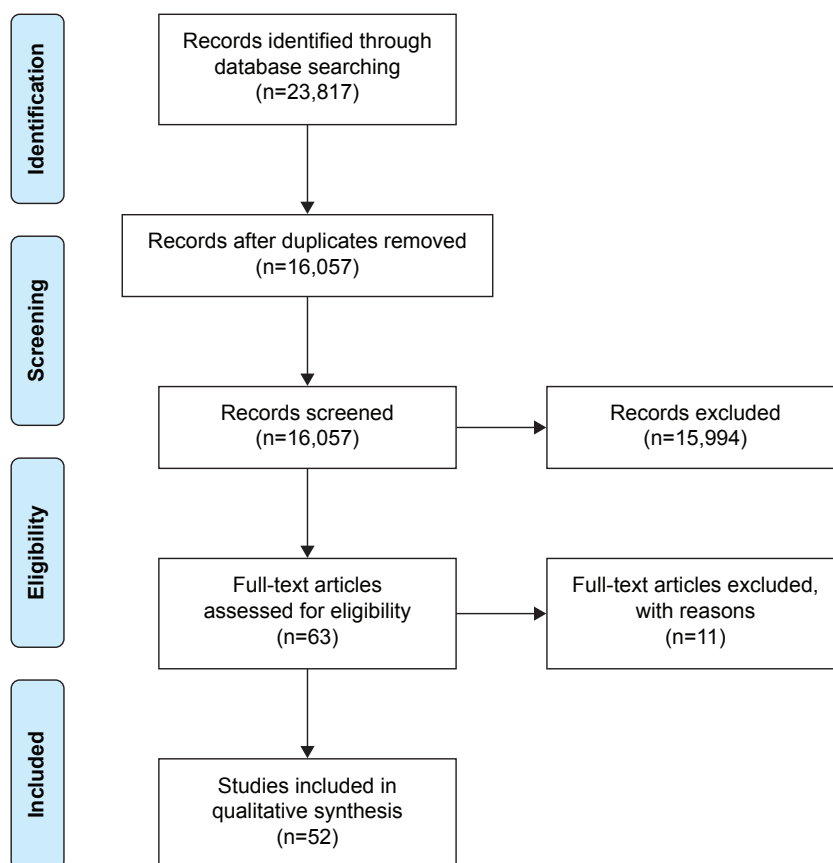
## Included studies

A total of 52 studies with 6,917 patients (range 15–591) were included. Studies were grouped according to the

type of pain investigated, including prevalence of pain in general, prevalence by location, including pain related to arteriovenous (AV) access, headache, limb pain, chest pain, abdominal pain, and “other and procedural” pain, as well as such causes of pain as musculoskeletal pain, ischemic pain, and neuropathic pain.

A total of 49 studies were observational, including one letter to the editor, which contained original data that were extracted.<sup>32</sup> Data about baseline pain prevalence were extracted from three interventional studies as well.<sup>33–35</sup> All studies were published in peer-reviewed journals except one, which was freely available on an institution’s Web site.<sup>35</sup>

Included studies were published between 1972 and 2014, and 39 of them were published in English. Studies were published in French,<sup>35–37</sup> Italian,<sup>38</sup> Portuguese,<sup>39,40</sup> Serbian,<sup>41,42</sup> and Spanish.<sup>43–47</sup> Studies were conducted mainly in Europe and North America (Table 2), while the remaining studies were conducted in South America,<sup>21,25,39,48–51</sup> Asia,<sup>33,52–54</sup> and Africa.<sup>24,37</sup> Distribution of age, ratio of male to female, and time on HD were very heterogeneous between the studies (Table 2). Race/ethnicity of patients was reported by only 13 studies (Table 2).



**Figure 1** Study flow diagram.

Table 2 Characteristics of included studies

Study	Language	Country	n	Average age (years) <sup>a</sup>	Sex: % of males	Time on HD <sup>a</sup>	Race/ethnicity (%)	Painful condition studied
Aitken et al <sup>55</sup>	English	Scotland	449	60.5±0.72	56.6	5.19±2.3 years (range 0–27) (time from creation of AVF)	Not reported	AVF pain: acute pain on cannulation and chronic pain between dialysis sessions (most days for at least 4 weeks)
Alessandri et al <sup>78</sup>	English	Italy	24	58±4 (range 41–75)	63	HDH patients: 37±3 months HDH-free: 45±4 months 34.5±2.7 months	Not reported	HDH (IHS 2004 criteria)
Al-Hilali et al <sup>33</sup>	English	Kuwait	40	48.6±14.9	38		Not reported	Intradialytic symptoms; baseline measure was used for this study
André et al <sup>21</sup>	English	Brazil	SHD 36 DHD 5	SHD 36±15 DHD 41±12	SHD 64 DHD 100	SHD 57±36 months DHD 50±21 months	B/W: SHD 19/17 DHD 2/3	Intradialysis symptoms during last 6 months, including headache
Antoniazzi et al <sup>39</sup>	Portuguese	Brazil	50	60% aged 20–49; 38% ≥50	56	42.4 months	Not reported	All patients had headaches strictly related to HD sessions (IHS 1988 criteria)
Antoniazzi et al <sup>48</sup>	English	Brazil	123	48.2	58	42.2 months	Not reported	All types of headache; HDH (IHS 1988 criteria)
Antoniazzi et al <sup>49</sup>	English	Brazil	132	Not reported	Not reported	Not reported	Not reported	All types of headache; HDH (IHS 1988 criteria)
Bana et al <sup>72</sup>	English	USA	44	38±19	73	Not reported	Not reported	All types of headache during HD
Barakzoy and Moss <sup>15</sup>	English	USA	143	Not reported for all participants	37	Not reported	White: 83 Black: 17	Current pain at the time of survey
Barrett et al <sup>79</sup>	English	Canada	147	54±17	61	3.7±3.2 years	Not reported	Somatic symptoms in HD patients (time recall for pain unclear)
Binik et al <sup>61</sup>	English	Canada	80 (53 HD, 27 Tx)	45.3	61	Range 1.4–2.8 years	Not reported	All types of pain on and off dialysis (time frame for reporting pain not reported)
Bouattar et al <sup>36</sup>	French	Morocco	67	43.5±12.9	42	122±67 months (range 3–312)	Not reported	Chronic pain of all types (duration above 3 months)
Bourbonnais and Tousignant <sup>57</sup>	English	Canada	25	31–80 68% >61	60	Range 3 months–30 years	Not reported	Pain either during HD or upon returning home
Braz and Duarte <sup>40</sup>	Portuguese	Brazil	162	47.3	58	44.1 months	Caucasian: 26 Non-Caucasian: 74	Musculoskeletal manifestations in HD patients (time recall for pain unclear)
Calls et al <sup>43</sup>	Spanish	Spain	27	66.7±13.6	48	66.4±61.3 months	Not reported	Intradialytic and chronic pain (definition of chronic pain not reported)
Caplin et al <sup>60</sup>	English	UK	508	Median 64	54	Median 37 months (range 18–64)	White: 45 Black: 29 South Asian: 20 Other: 2	Symptoms specifically experienced during the HD session
Caplin et al <sup>34</sup>	English	UK	519	63 (range 50–75)	56	Median 32 months (range 13–52.5)	White: 37 Black: 34 South Asian: 15 Chinese: 7 Other: 7	All symptoms specifically experienced during the HD session

Carreon et al <sup>80</sup>	English	USA	75	59±14	67	4.4±5.8 years	White: 64	Bone/joint pain over the past 7 days
Chattopadhyay et al <sup>81</sup>	English	UK	15	Median 45 (range 31–59)	73	182 months (range 120–210)	Not reported	Shoulder-pain syndrome on long-term HD (time frame for reporting pain not reported)
Claxton et al <sup>82</sup>	English	USA	62	59	55	4±4 years	White: 26 African-American: 35	Physical symptoms over the prior week
Cristofolini et al <sup>50</sup>	English	Brazil	205	51.9±14.8	51	Median (range) With LBP: 2.8 years (0–17) Without LBP: 1.5 years (0–29)	Not reported	Chronic LBP (duration above 3 months)
Davison <sup>14</sup>	English	Canada	205	60±16.9	58	45.0±38.5 months	Caucasian: 78.5 Asian: 7.8 First Nations: 6.3 African: 1.5 Other: 5.9	Chronic pain of all types (duration above 3 months), pain in previous 24 hours, and current pain
Davison et al <sup>82</sup>	English	Canada	205	60±16.9	58	33.2±49.4 months Median 15.6 months	Caucasian: 78.4 Asian: 7.8 First Nations: 6.4 African: 1.5 Other: 5.9	Chronic pain of all types (duration above 3 months)
Davison et al <sup>83</sup>	English	Canada	591	61.3±16.3	9.3	3.3±2.8 years	White: 72.6 Aboriginal: 11.3 Others: 16.1	Dialysis patients' symptom burden, including pain (time frame for reporting pain not reported)
Jesus et al <sup>51</sup>	English	Brazil	177	46.22±14.3	59	32.9±22.8 months	Not reported	All types of headache; HDH (IHS 2004 criteria)
Armendáriz et al <sup>44</sup>	Spanish	Spain	35	Not reported	Not reported	Not reported	Not reported	Evaluation of pain before, during, and after dialysis
Djurić et al <sup>41</sup>	Serbian	Serbia	143	Range 20–86	65	HDH patients: 57.2±60.4 months HDH-free: 49.2±44.1 months	Not reported	All types of headache, HDH (IHS 2004 criteria)
El Harraqui et al <sup>37</sup>	French	Morocco	66	55.3±13.3	45	82±56 months (range 4–252)	Not reported	Pain's epidemiology and characteristics in chronic HD, including AVF puncture pain
Elsurer et al <sup>84</sup>	English	Turkey	95	53.9±14.3 (range 20–82)	52	Median 48 months (range 15–300)	Not reported	Chronic bone pain (>3 months)
Er et al <sup>85</sup>	English	Turkey	95	51.5 (range 22–78)	Not reported	5.21±3.89 years	Not reported	Pain in HD patients: instant (24 hours), acute (>3 days), and chronic (>3 months)
Fidan et al <sup>86</sup>	English	Turkey	50	56.04±16.77	48	Median 24 months (range 2–276)	Not reported	All patients had MS symptoms at the time of the study
Fortina et al <sup>38</sup>	Italian	Italy	100	68±33 (range 33–88)	73	Not reported	Not reported	Chronic pain of all types (definition of chronic pain not reported)

(Continued)

Table 2 (Continued)

Study	Language	Country	n	Average age (years) <sup>a</sup>	Sex: % of males	Time on HD <sup>a</sup>	Race/ethnicity (%)	Painful condition studied
Gamondi et al <sup>87</sup>	English	Switzerland	123	Range 36–90	61	3.5 years (range 1–22)	Not reported	Pain during the past 4 weeks
Goksan et al <sup>88</sup>	English	Turkey	63	44±10	52	5±3.8 years	Not reported	All patients HDH (IHS 1988 and 2003 criteria)
Goksel et al <sup>59</sup>	English	Turkey	250	44.9±16.9 (range 15–75)	42	HDH patients: 47.7±42 months Control: 41.3±32 months	Not reported	Prevalence of all types of headache; further studies only patients with headache experiences during HD sessions and in the 72 hours after a session (IHS 2004 criteria)
Golan et al <sup>52</sup>	English	Israel	100	64.5	45	40.4±42.0 months (range 3–204)	Arab: 31 Non-Arab: 69	Chronic pain (duration above 3 months)
Harris et al <sup>89</sup>	English	USA	128	57.3±13.8 (range 24–86)	60.2	39.9±40.9 months	African-American: 91.4 White: 7	Pain during HD treatment (excluding needle insertion) and at times between dialysis treatment (nondialysis days) during past month
Iacono et al <sup>90</sup>	English	USA	45	53	Not reported	4.2 years	Asian or Pacific Islander: 1.6	In-center HD chronic pain
Khan et al <sup>91</sup>	English	Pakistan	42	Range 20–75	64	Not reported	Not reported	Symptomatology in ESRD patients on HD
Kimmel et al <sup>92</sup>	English	USA	165	60.9	52	44 months	African-American: 33.3 White: 63 Asian: 1.2 Other: 2.5	Symptoms of patients on HD, including pain (time frame for reporting pain not reported)
Konishiike et al <sup>53</sup>	English	Japan	166	58.4 (range 35–78)	57	9 years (range 0.3–22.7)	Not reported	Shoulder pain at the time of survey in long-term HD patients
Malaki et al <sup>54</sup>	English	Iran	26	35.7±21.9	23	34.8±18 months (range 9–75 months)	Not reported	Leg pain present at least for three to four times per week, persisting for several weeks
Mercadante et al <sup>32</sup>	English	Italy	95	63.4±14.4	41.8	5±4.5 years	Not reported	Chronic pain (IASP 1986 criteria)
Millinković et al <sup>58</sup>	English	Serbia	318	55.19±15.5	63	HDH patients: 49.43±39.56 months HDH-free: 55.63±53.2	Not reported	All types of headache; HDH (IHS 2004 criteria)
Nikić et al <sup>42</sup>	Serbian	Serbia	126	58 (range 20–79)	62	HDH patients: 73.34±63.29 months HDH-free: 59.01±53.17	Not reported	All types of headache; HDH (IHS 2004 criteria)
Parfrey et al <sup>93</sup>	English	Canada	77	52±2	53	3.5±0.4 years	Not reported	Nonspecific symptoms currently experienced in dialysis patients, including headache
Rodriguez Calero et al <sup>46</sup>	Spanish	Spain	38	65±14.8	47	65.13±78.5 months	Not reported	Current intradialytic pain
Rodriguez Calero et al <sup>45</sup>	Spanish	Spain	32	66.7±13.6	53	Pain patients: 61.5±60.3 months Pain-free: 47.8±43.8 months	Not reported	Chronic pain of all types (definition of chronic pain not reported)

Rodriguez Calero et al <sup>47</sup>	Spanish	Spain	27	66.7±13.6	48	Pain patients: 60.5±58.5 Pain-free: 45.7±44.2 months	Not reported	Not reported	Chronic and intradialytic pain (definition of chronic pain not reported)
Shayamsunder et al <sup>94</sup>	English	USA	156	Not reported	Not reported	Not reported	Not reported	Pain in the HD population, including pain on needle insertion (no details about the type of cannulation or pain reporting period)	
Vergne et al <sup>35</sup>	French	France	66	66.8±13.1	73	47 months, median 25 months	Not reported	Not reported	AV-access puncture pain (rope-ladder technique)
Weisbord et al <sup>95</sup>	English	USA	179	61.9	62	4±4.1 years	Black: 48 White: 51 Asian: 1	Symptoms, including pain, in previous 7 days	

**Note:** \*Average age and time on hemodialysis presented as mean ± SD, unless indicated differently.

**Abbreviations:** AV, arteriovenous; AVF, arteriovenous fistula; B/W, black/white ratio; DHD, daily hemodialysis; ESRD, end-stage renal disease; HD, hemodialysis; HDH, HD headache; IASP, International Association for the Study of Pain; IHS, International Headache Society; LBP, low-back pain; MS, musculoskeletal; SD, standard deviation; SHD, standard HD; Tx, transplant.

## Prevalence and severity of pain in general

Nineteen studies with 2,377 patients (range 27–591) that were included examined the general prevalence of pain, both chronic and acute, in the analyzed cohorts of HD patients (Table 3). The reported prevalence of chronic pain ranged from 33% to 82%, while the prevalence of acute pain (current pain, intradialytic pain, pain during the past 4 weeks) ranged from 21% to 92% (Table 3).

Rodriguez Calero et al showed very high prevalence of intradialytic pain, with only 8% of patients reporting no pain at all. Analgesics were prescribed to 18% of patients, and the Pain Management Index (PMI) showed clear undertreatment of pain, which was more accentuated among patients who reported more intense pain.<sup>46</sup>

Characteristics of pain were reported by only a few studies. Bouattar et al reported that patients described their chronic pain as continuous (21%), frequent (18%), intermittent (47%), and rare (15%).<sup>36</sup> Severity of pain in general was reported with various pain scales in all studies except one. The pain-assessment scales used in studies reporting general pain were the short-form McGill Pain Questionnaire (MPQ), visual analog scale (VAS), PMI, Brief Pain Inventory, modified Edmonton Symptom Assessment System, and the McGill–Melzack Pain Questionnaire (Table 3). While the average reported pain intensity tended to be low, multiple studies indicated high prevalence of patients with moderate or severe pain (Table 3). Reported prevalence of severe/intensive pain ranged from 0%<sup>45</sup> to 76%.<sup>15</sup>

## Prevalence and severity of AV-access pain

In the included studies, pain related to AV access was described in various terms, relating not only to AV fistula (AVF), which is why the broader term “AV access” is used herein to describe pain reported in these studies.

Ten studies with a total of 1,028 patients (range 25–449) analyzed prevalence and/or severity of pain related to AV access (Table 4). If available, type of AV access was extracted (Table 4). Only two studies provided details about AV access. Aitken et al<sup>55</sup> indicated that there was a trend toward more severe pain with rope-ladder cannulation (27.7%) compared to buttonhole cannulation (18.2%); however, this difference did not reach statistical significance ( $P=0.09$ ). In Vergne et al, some patients had rope-ladder cannulation of AVF, but some also had a graft.<sup>35</sup>

The majority of studies were observational, with two interventional studies reporting baseline pain intensity.<sup>35,56</sup> The prevalence of acute and chronic pain or both was studied, ranging from 12%<sup>57</sup> to 80.2%<sup>52</sup> (Table 4). Severity of pain was not always reported. Different pain-assessment scales

**Table 3** Characteristics of studies reporting general pain in HD patients

Study	Painful condition studied	Prevalence of general pain (%)	Pain-intensity measurement tool	Pain-intensity results
Barakzoy and Moss <sup>15</sup>	Current pain of all types at the time of survey	54	SF-MPQ (VAS)	Current pain Moderate or severe: 86% Initial pain Severe: 76% Chronic pain Low: 3% Moderate: 41% Severe: 44 Very severe: 12% Intradialytic vs chronic pain VAS: 3.28±2.22 vs 2.67±2.13 PMI: 0.81±0.76 vs -0.12±0.94 MPQ: similar in both situations
Bouattar et al <sup>36</sup>	Chronic pain of all types (duration above 3 months)	50.7	Descriptive verbal scale	Previous 24 hours Mild (0–4): 17.5 Moderate (5–6): 27.2 Severe (7–10): 55.3 (BPI 7.03±2.40)
Calls et al <sup>43</sup>	Intradialytic and chronic pain of all types (definition of chronic pain not reported)	During the session: 92.5 Off-session: 77.7	VAS, MPQ, PMI	Current Mild: 44.7 Moderate: 28.2 Severe: 55.3 (BPI 4.99±2.96)
Davison <sup>14</sup>	Chronic pain of all types, (duration above 3 months), pain during past 24 hours, current pain	50	BPI, MPQ	MPQ PRI 22.2±13.8, PPI 2.6±1.6, NWC 8.7±5.2 Moderate or severe: 41.4%
Davison et al <sup>82</sup>	Chronic pain of all types (duration above 3 months)	50.2	BPI	Moderate or severe: 46.5%
Davison et al <sup>83</sup>	Dialysis patients' symptom burden, including pain (time frame for reporting pain not reported)	72.4	mESAS	VAS results not reported Not specified whether instant or chronic
Armendáriz et al <sup>44</sup>	Evaluation of pain before, during, and after dialysis	71.4	VAS	Mild: 28.3
Er et al <sup>85</sup>	Instant pain (24 hours), acute (>3 days), and chronic (>3 months)	63.1 A: 26 C: 33	MMPQ	Disturbing: 23.3 Severe: 31.7 Very severe: 10 Intolerable: 6.7 Previous 4 weeks Mild: 17% Moderate: 21% Intense: 61% At the time of interview
Gamondi et al <sup>87</sup>	Pain during the past 4 weeks	66	VAS and BPI	

Golan et al <sup>52</sup>	Chronic pain (duration above 3 months)	51	BPI	No pain: 68% Mild: 16% Moderate: 8.5% Intense: 6% Chronic pain Mild: 49% Moderate: 31.4% Severe: 19.6% During dialysis: 2.1±3.5 Highest level of pain: 3.9% Between dialyses: 3.1±3.8 Highest level of pain: 7.9% NA
Harris et al <sup>89</sup>	Pain during HD treatment (excluding needle insertion) and at times between dialysis treatment (nondialysis days) during past months	HD: 30.7 Off HD: 44.1	Modified MPQ	
Kimmel et al <sup>92</sup>	Symptoms of patients on HD, including pain (time frame for reporting pain not reported)	21	Not measured	
Mercadante et al <sup>32</sup>	Chronic pain (IASP 1986 criteria)	48	NRS	5.59±1.63 (95% CI 5.12–6.03)
Rodriguez Calero et al <sup>46</sup>	Intradialysis pain of all types	92	VAS, MPQ, PMI	Intradialysis pain: 3.31±2.22
Rodriguez Calero et al <sup>45</sup>	Chronic pain of all types (definition of chronic pain not reported)	82	VAS, MPQ, PMI, BPI	Chronic pain: 2.41±2.13
Rodriguez Calero et al <sup>47</sup>	Chronic and intradialytic pain of all types (definition of chronic pain not reported)	ID: 92 C: 78	VAS, MPQ, PMI, BPI	Severe (VAS >7.5): no case reported ID: 3.28±2.22 C: 2.67±2.13
Shayamsunder et al <sup>94</sup>	Pain in ESRD patients treated with chronic HD	During HD: 30 On non-HD days: 44	Not measured	NA
Iacono et al <sup>90</sup>	In-center HD chronic pain	60	5-point Likert scale	Mean 3.3
Fortina et al <sup>38</sup>	Chronic pain of all types (definition of chronic pain not reported)	37	VAS	Not reported for general pain

**Abbreviations:** A, acute; BPI, Brief Pain Inventory; C, chronic; CI, confidence interval; ESRD, end-stage renal disease; HD, hemodialysis; IASP, International Association for the Study of Pain; ID, intradialytic pain; mESAS, modified Edmonton Symptom Assessment System; MPQ, McGill Pain Questionnaire; MMPQ, McGill-Melzack Pain Questionnaire; NA, not applicable; NRS, numeric rating scale; NWC, number of words chosen; PMI, Pain Management Index; PPI, present pain intensity; PRI, Pain Rating Index; SF-MPQ, short-form McGill Pain Questionnaire; VAS, visual analog scale.

**Table 4** Type of pain studied, prevalence and assessment tools for AV-access pain

Study	Timing and type of AV-access pain studied	Type of cannulation	Prevalence of AV-access pain (%)	Pain-assessment tool for AV-access pain	Pain-intensity results
Aitken et al <sup>55</sup>	Both acute pain (on cannulation) and chronic pain (between dialysis sessions, most days for at least 4 weeks) related to AVF	Rope-ladder; buttonhole	Any pain AP 25 CP 50 Severe (VAS >5) AP 24 CP 3.2	VAS, BPI, and MPQ	Pain on cannulation Median 3 (IQR 0.5–4.5) Severe pain 24.4% Between dialyses 0 (IQR 0–1) Severe pain 3.2% On HD 3.6
Binik et al <sup>61</sup>	Acute (current) pain related to fistula	Not reported	On HD 15 Dialysis pain reported by post-Tx 7.4	Structured interview and MPQ	NA
Bourbonnais and Tousignant <sup>57</sup> Calls et al <sup>43</sup>	Acute needling pain from both insertion of needle and removal Both acute intradialytic and chronic pain related to vascular access	Not reported	12	Not measured	NA
El Harraqui et al <sup>37</sup>	Definition of chronic pain not reported Chronic pain associated with vascular access Chronic pain defined as pain of >3 months' duration	Not reported	AP 21.9 CP 21.8	Not measured	NA
Golan et al <sup>52</sup>	Pain related to repeated dialysis access cannulation as a form of chronic pain (needle insertion in patients with a fistula or graft)	Not reported	80.2	Not measured	NA
Rodriguez Calero et al <sup>46</sup>	Acute intradialytic assessment of pain related to vascular access	Not reported	21	Not measured	NA
Rodriguez Calero et al <sup>47</sup>	Chronic pain related to vascular access	Not reported	37	Not measured	NA
Shayamsunder et al <sup>44</sup>	Pain in ESRD patients treated with chronic HD, including acute intradialytic pain on needle insertion	Not reported	78.4	Not measured	NA
Vergne et al <sup>35</sup>	Acute AVF (natural or PTFE graft) puncture pain	Rope-ladder	57.5	NRS	Low pain 79% Moderate 13% Severe 8%

**Abbreviations:** AP, acute cannulation pain; AV, arteriovenous; AVF, arteriovenous fistula; BPI, brief pain inventory; CP, chronic cannulation pain; ESRD, end-stage renal disease; HD, hemodialysis; IQR, interquartile range; MPQ, McGill Pain Questionnaire; NA, not applicable; NRS, numeric rating scale; PTFE, polytetrafluoroethylene; Tx, transplant; VAS, visual analog scale.

were used, including the MPQ, VAS, Brief Pain Inventory, PMI, and numeric rating scale.

## Prevalence and severity of headache

A total of 24 studies with 3,444 patients (range 24–519) analyzed prevalence and/or severity of headache in HD patients. Some studies looked for headache as part of the overall symptom burden in HD patients; a subset of studies analyzed different types of headache in HD patients, while some analyzed specifically HD headache (HDH) (Table 5). Two studies were interventional,<sup>33,34</sup> and prevalence of headache before the intervention was reported for those studies. The other studies were observational.

Reported prevalence rates of headache in HD patients varied considerably. For presentation of these results, it is important to emphasize that some studies reported prevalence of all headaches, while others reported specifically prevalence of HDH according to International Headache Society (IHS) diagnostic criteria. Some studies reported both. The reported prevalence of all kinds of headaches ranged from 11.8%<sup>36</sup> to 76.1%.<sup>51</sup> The reported prevalence of HDH, diagnosed according to the 1988 or 2004 IHS criteria, ranged from 6.6%<sup>58</sup> to 68%<sup>39</sup> (Table 5).

Severity of headache was assessed with various scales, including descriptive scales, the MPQ, and the VAS. Different severity of headache was observed in the included studies, indicating that headache pain can be very debilitating. Analyzing types of headache, Goksel et al reported average pain intensity on the VAS as  $6.06 \pm 2.4$ .<sup>59</sup> The prevalence of severe pain ranged from 36%<sup>51</sup> to 88%<sup>41</sup> (Table 5).

## Prevalence of limb pain

Six studies with 422 patients (range 26–205) reported the prevalence of lower- and/or upper-limb pain without analyzing causes of that pain. Studied pain was chronic, acute, or both (Table 6). The reported prevalence of chronic lower-leg pain was very similar in the three studies examining this type of pain, while the prevalence of lower-leg pain lasting several weeks was 42% and current intradialytic pain reported by 34% of patients in the three studies that examined it. Chronic upper-limb pain prevalence was more heterogeneous (Table 6). A sixth study reported the prevalence of chronic peripheral neuropathy as 13% without specifying the affected body part.<sup>14</sup> None of the studies reported pain severity of limb pain.

**Table 5** Studies of headache prevalence

Study	Timing and type of headache studied	Prevalence of headache (%)	Pain-assessment tool for headache	Pain-intensity results
Alessandri et al <sup>78</sup>	HDH (IHS 2004 criteria)	HDH: 50	Not described in methods	Most patients had mild or moderate severity of pain
Al-Hilali et al <sup>33</sup>	Intradialytic symptoms, including headache; baseline measure was used for this study	Hi: 37.5 (before the intervention)	Not measured	NA
André et al <sup>21</sup>	Intradialysis symptoms during last 6 months, including headache	Hi: 13	Not measured	NA
Antoniazzi et al <sup>39</sup>	All patients had headaches strictly related to HD sessions (IHS 1988 criteria)	Hi: 70.7 HDH: 68 (in the second half of HD: 86)	Not measured	NA
Antoniazzi et al <sup>48</sup>	All types of headache; HDH (IHS 1988 criteria)	Hi: 70.7 (during HD: 57.5) HDH: 28 HDH: 21.2 Hi: 70	Not measured	NA
Antoniazzi et al <sup>49</sup> Bana et al <sup>72</sup>	All types of headache; HDH (IHS 1988 criteria) All types of headache during HD		Not measured Descriptive measure of headache severity Perception of symptom severity	NA An average of 6 headache units per dialysis Mentioned in methods, but results not reported
Barrett et al <sup>79</sup>	Somatic symptoms in HD patients, including headache (time recall for pain unclear)	Hi: 45		

(Continued)

Table 5 (Continued)

Study	Timing and type of headache studied	Prevalence of headache (%)	Pain-assessment tool for headache	Pain-intensity results
Binik et al <sup>16</sup>	All types of pain on and off dialysis, including headache	On HD: 62.3 Off HD: 43 Reported by post-Tx: 66.7 H: 11.8	MPQ	On HD 6.2 Off HD 7
Bouattar et al <sup>16</sup>	Chronic pain of all types, including headache		Descriptive verbal scale	Low 3% Moderate 41% Severe 44% Very severe 12% NA
Calls et al <sup>43</sup>	Intradialytic and chronic pain, including headache	IH: 31.5 CH: 6.2 IH: 53.6	Not measured	NA
Caplin et al <sup>60</sup>	Symptoms specifically experienced during the HD session, including headache		Not measured	NA
Caplin et al <sup>34</sup>	All symptoms specifically experienced during the HD session	IH: 56 H: 76.1	Not measured	NA
Jesus et al <sup>51</sup>	All types of headache; HDH (IHS 2004 criteria)	HDH: 6.7 H: 19 HDH: 5.6 H: 31	VAS	Moderate 63.6% VAS $\geq 8$ (severe) 36.4% VAS $> 8$ (severe) 87.5%
Djurić et al <sup>41</sup>	All types of headache; HDH (IHS 2004 criteria)		VAS	
Gamondi et al <sup>67</sup>	Pain duration, intensity, perception, and localization in patients reporting pain during the 4 weeks before the interview		Not measured	NA
Goksan et al <sup>68</sup>	All patients HDH (IHS 1988 and 2003 criteria)	HDH: 48	Descriptive scale for intensity of headache	Moderate 73% Severe 27% Very severe 87% Mean $\pm$ SD 6.06 $\pm$ 2.4
Goksel et al <sup>69</sup>	Prevalence of all types of headache; further studies, only patients with headache experiences during HD sessions and in the 72 hours after a session; IHS 2004 criteria	HDH: 30	VAS	
Golan et al <sup>52</sup>	Chronic pain (lasting 3 months and more), including headache	CH: 54.9	Not measured	NA
Milinković et al <sup>58</sup>	All types of headache; HDH (IHS 2004 criteria)	HDH: 6.6 H: 32.5	VAS	Severe (VAS $> 8$ ) 52% Mild 14.3%
Nikić et al <sup>42</sup>	All types of headache; HDH (IHS 2004 criteria)	HDH: 34	VAS	Moderate 50% Severe (VAS $> 8$ ) 35.7%
Parfrey et al <sup>93</sup>	Nonspecific symptoms experienced in dialysis patients, including headache	H: 41 (during or just after HD 56)	Not reported for HD patients separately	NA
Rodriguez Calero et al <sup>47</sup>	Intradialytic and chronic pain, including headache	IH: 31.5 CH: 6.2 H: 19	Not measured	NA
Weisbord et al <sup>95</sup>	Physical and emotional symptoms in maintenance-HD patients, including headache		DSI	Mean 3.03

**Abbreviations:** CH, chronic headache; DSI, Dialysis Symptom Index; H, headache; HD, hemodialysis; HDH, HD headache; IH, intradialytic headache; IHS, International Headache Society; MPQ, McGill Pain Questionnaire; NA, not applicable; Tx, transplant; VAS, visual analog scale.

**Table 6** Prevalence of limb pain

Study	Painful condition studied	Prevalence of limb pain (%)
Bouattar et al <sup>36</sup>	Chronic pain of all types (duration above 3 months), including upper- and lower-limb pain	UL 74 LL 62
Calls et al <sup>43</sup>	Intradialytic and chronic pain (definition of chronic pain not reported), including upper- and lower-limb pain	LL: ID 34, C 63 UL: ID 11, C 19
Davison <sup>14</sup>	Chronic pain (duration above 3 months), including painful PN	PN 13
Malaki et al <sup>54</sup>	Leg pain present at least three to four times per week, persisting for several weeks	LL 42
Rodriguez Calero et al <sup>46</sup>	Current intradialytic pain	LL 34
Rodriguez Calero et al <sup>45</sup>	Chronic pain of all types (definition of chronic pain not reported), including lower-limb pain	LL 63
Rodriguez Calero et al <sup>47</sup>	Intradialytic and chronic pain (definition of chronic pain not reported), including upper- and lower-limb pain	UL: ID 10.5, C 18.7 LL: ID 34.2, C 62.5

**Abbreviations:** C, chronic; ID, intradialytic; LL, lower limb; PN, peripheral neuropathy; UL, upper limb.

## Prevalence and severity of musculoskeletal pain

A total of 21 studies with 2,778 patients (range 15–519) reported the prevalence of musculoskeletal pain in HD patients (Table 7). The studies reported different types of pain, ranging from carpal tunnel syndrome to muscle cramps. Data on pain severity for musculoskeletal pain indicated that such pain can be considerable (Table 7).

## Prevalence of chest pain

Six studies with 747 patients (range 27–508) reported the prevalence of chest pain in HD patients.<sup>36,43,46,47,60,61</sup> Two studies reported the prevalence of intradialytic pain as exactly 2.6%,<sup>43,46</sup> while the third found chest pain during HD sessions to be 25%.<sup>60</sup> Chronic chest pain was reported to be 5.9%<sup>36</sup> and 9.3%.<sup>43</sup> Binik et al reported chest pain both on and off dialysis in 13% of the sample.<sup>61</sup> Only Binik et al reported pain severity using MPQ score as 6.4 on dialysis and 6.9 off dialysis.<sup>61</sup>

## Prevalence and severity of abdominal pain

Six studies reported the prevalence of abdominal pain.<sup>36,43,46,47,52,61</sup> Prevalence of intradialytic abdominal pain was reported as 16% in two studies,<sup>43,46</sup> chronic abdominal pain as 18% in two studies<sup>36,52</sup> and 9.3% in one study.<sup>43</sup> Binik et al reported the prevalence of abdominal pain both on and off dialysis as 17%.<sup>61</sup> Only one study reported the severity of abdominal pain as being 7.3 on MPQ score for on-HD abdominal pain.<sup>61</sup>

## Prevalence of other pain

Several studies reported the prevalence of “other” pain, but this type of pain was rarely specified. Golan et al reported

that 13% of patients had chronic pain from various other sources, such as phantom pain, steal syndrome, and nonspecific diffuse pain.<sup>52</sup> Davison found prevalence of other combined chronic pain (including trauma, polycystic kidney disease, malignancy, and calciphylaxis) to be 18.4%.<sup>14</sup> Claxton et al reported the prevalence of other pain over the prior week as 18%, but without specifying any details about the location or causes of that pain.<sup>62</sup> Calls et al<sup>43</sup> and Rodriguez Calero et al<sup>47</sup> (using the same raw data) reported the prevalence of other (polycystic kidney disease, neoplasia) pain during HD sessions as 3.7% and chronic pain as 7.4%. Severity of pain listed as “other” was not reported in these studies.

## Prevalence of procedural pain

Five studies reported the prevalence of poorly defined “procedural pain”.<sup>14,43,45–47</sup> Calls et al reported that 26% of patients suffered from procedural pain, including cramps, headaches, and pain related to vascular access.<sup>43</sup> Davison reported that 6.8% of patients experienced significant pain due to recurrent symptoms related to HD that included “cramping, headaches, and access-related pain, such as pain from needling fistulas and pain in the fistula hand”. This represented 14% of patients reporting a problem with pain.<sup>14</sup> Rodriguez Calero et al reported that 25.9% patients identified the procedure itself as the cause of the pain,<sup>47</sup> while another study showed a slightly higher prevalence (29%).<sup>46</sup> Finally, according to their most recent results, 38% suffered from procedure-related pain.<sup>45</sup> Therefore, while three studies did not explain what procedural pain was,<sup>45–47</sup> the other two explained that procedural pain can have different locations and causes,<sup>14,43</sup> which were reported as specific types of pain in other studies included in this review.

Table 7 Studies of MS-pain prevalence and intensity

Study	Timing and type of MS pain studied	Prevalence of MS pain (%)	Pain-assessment tool for MS pain	Pain-intensity results
Al-Hilali et al <sup>33</sup>	Intradialytic symptoms, including muscle cramps; baseline measure was used for this study	Cramps: 23	Not measured	NA
André et al <sup>21</sup>	Intradialysis symptoms during last 6 months, including cramps	Cramps: 18 (type of cramps not specified)	Not measured	NA
Barrett et al <sup>79</sup>	Somatic symptoms in HD patients, including joint pain and cramps; time recall for pain not reported	Joint pain: 43	Not measured	NA
Binik et al <sup>61</sup>	All types of pain on and off dialysis, including cramps and bone pain	Cramps: 53 (type of cramps not specified) On HD: cramps 81, bone 11 Off HD: cramps 62, bone 15, back 5.7	MPQ	On HD: cramps 10.7, bone 11.3 Off HD: cramps 9.9, bone 8.4, back
Bouattar et al <sup>36</sup>	Chronic pain of all types (duration above 3 months)	Post-Tx reporting dialysis pain: cramps 51.9, bone 3.7 OA: 76.5	Not measured	NA
Bourbonnais and Tounignant <sup>57</sup>	Pain during either HD or upon return home	Posttraumatic: 2.9	Not measured	NA
Braz and Duarte <sup>40</sup>	MS manifestations in HD patients (time recall for pain unclear)	Cramps and muscle pain: 25 Joint and back pain: 1,456 Arthralgia: 16	Not measured	NA
Calls et al <sup>43</sup>	Intradialytic and chronic pain (definition of chronic pain not reported)	Bone pain: 7 CTS: 1 Myalgia: 2 MS pain ID: 33 C: 77 CTS: ID: 3.7 C: 7.4 Backache ID: 28.9 C: 37.5	Not measured	NA
Caplin et al <sup>60</sup>	Symptoms specifically experienced during the HD session	Cramps: 74 (type of cramps not specified)	Not measured	NA
Caplin et al <sup>34</sup>	All symptoms specifically experienced during the HD session	Backache: 51 Cramps: 74.3 (type of cramps not specified)	Not measured	NA
Carreon et al <sup>80</sup>	Bone/joint pain over the past 7 days	Bone/joint pain: 37	DSI (Likert scale 1–5)	Median: 3±1 Distribution 0–1 (no pain) 0 1–2 (mild) 29% 2–3 (moderate) 36% 3–4 (severe) 21% 4–5 (excruciating) 14%

Chattopadhyay et al <sup>81</sup>	SP syndrome on long-term HD (time frame for reporting pain not reported)	SP: 67 CTS: 73 KP: 7	Not measured	NA
Claxton et al <sup>62</sup>	Physical symptoms over the prior week	Bone/joint pain: 53	DSI; Likert scale 0–4	2.8 for bone/joint pain
Cristofolini et al <sup>50</sup>	Chronic LBP (duration above 3 months)	LBP: 36	Not measured	NA
Davison <sup>14</sup>	Chronic pain of all types (duration above 3 months)	MS: 63 CTS: 1.9	Not measured	NA
Elsurer et al <sup>84</sup>	Chronic bone pain (duration above 3 months)	Bone pain: 52	VAS	VAS (mean $\pm$ SD) 39.8 $\pm$ 32.1
Fidan et al <sup>86</sup>	All patients had MS symptoms at the time of the study	Arthralgia: 60 Myalgia: 62 Cramps: 82 Bone pain: 48 OA: 24	VAS	VAS hand (mean $\pm$ SD) 2.58 $\pm$ 2.51 VAS upper extremities (mean $\pm$ SD) 2.58 $\pm$ 2.51
Fortina et al <sup>38</sup>	Chronic pain of all types (definition of chronic pain not reported)		VAS (0–4)	Mean score by different scorers Patients 3 Physicians 1.9 Paramedics 1 NA
Gamondi et al <sup>87</sup>	Pain during the past 4 weeks	MS: 64 Cramps: 25 BP: 26 OMP: 22 CJP: 12 CJP: 59 BP/NP: 55 Legs/feet: 55 Hands/arms: 37	Not measured	NA
Golan et al <sup>52</sup>	Chronic pain (duration above 3 months)	Bone pain: 52 Cramps: 40 SP: 36	Not measured	NA
Iacono et al <sup>90</sup>	In-center HD chronic pain	MS: ID 33, C 77 CTS: ID 3.7, C 7.4 Backache: ID 28.9, C 37.5	Not measured	NA
Khan et al <sup>91</sup>	Symptomatology in ESRD patients on HD		Not measured	NA
Konishiike et al <sup>53</sup>	Shoulder pain at the time of survey in long-term HD patients		Not measured	NA
Rodriguez Calero et al <sup>47</sup>	Intradialysis and chronic pain (definition of chronic pain not reported), including CTS, backache and MS pain		Not measured	NA

**Abbreviations:** BP, back pain; C, chronic; CJP, chronic joint pain; CTS, carpal tunnel syndrome; DSI, Dialysis Symptom Index; ESRD, end-stage renal disease; HD, hemodialysis; ID, intradialytic; KP, knee pain; LBP, low-back pain; MPQ, McGill Pain Questionnaire; MS, musculoskeletal; NA, not applicable; NP, neck pain; OA, osteoarthralgia; OMP, other MS pain; SD, standard deviation; SP, shoulder pain; Tx, transplant; VAS, visual analog scale.

## Prevalence of ischemic pain

Prevalence of ischemic pain as a cause of pain was reported in three studies.<sup>43,45,46</sup> In a study on current dialytic pain, with a prevalence of 32% it was reported as the most prevalent cause of pain,<sup>46</sup> while in another study on intradialytic ischemic pain its prevalence was even higher – 37%.<sup>43</sup> Prevalence of ischemic pain as a cause of chronic pain was reported as 25%<sup>45</sup> and 30%.<sup>43</sup>

## Prevalence of neuropathic pain

According to the literature, while a high percentage of HD patients have shown electrophysiological evidence of nerve damage, only a small proportion have been reported as suffering from neuropathic pain.<sup>63–65</sup> Generally, it occurs more frequently in males. Only three studies reported the prevalence of neuropathic pain.<sup>14,15,52</sup> The older the study was, the higher the prevalence shown. Davison reported a prevalence of neuropathic pain as 12.6%.<sup>14</sup> Three years later, Barakzoy and Moss reported it as 31%,<sup>15</sup> while Golan et al yielded a figure of 41.2%.<sup>52</sup>

## Quality of included studies

The STROBE checklist indicated that 49 observational studies were generally of moderate quality: scores ranged in sum from 6 to 18, with a median of 13 points. Three interventional studies assessed using the Cochrane risk-of-bias tool had high or unclear risk of bias in six of seven domains. Conflict of interest in the included studies was reported in only eleven of 52 studies: nine acknowledged support from public governmental grants/institutions or a private foundation; one indicated support from a small educational grant, but the source of the grant was not mentioned; while one study simply indicated that there was no conflict of interest.

## Discussion

The results of this systematic review offer a comprehensive view of epidemiological studies on pain in HD patients, indicating that pain can be very prevalent and severe in HD patients. Although some studies did not examine pain as a single concept, but reported specifically pain affecting certain body parts, such as headache or musculoskeletal pain, a uniform conclusion of the included studies indicates that pain is very prevalent in HD patients.

We found that the prevalence of acute and chronic pain in HD patients can be up to 82% and 92%, respectively, which is consistent with previous research. A previously published systematic review of symptom prevalence in ESRD, which included 59 studies, reported a mean HD-pain

prevalence of 47% (8%–82%).<sup>66</sup> Identifying prevalence rates has pertinent implications for investigating the fundamental pathophysiology and developmental pathways of pain in HD. Beyond reporting prevalence of general pain, the prevalence of various types of pain in HD patients was also reviewed in this study. Most of the studies reported the prevalence of pain related to AV access, headache, and musculoskeletal pain.

Pain related to AV access is a particular type of pain that can be expected in all HD patients. Vascular access is required to permit HD. AVF is the most effective and efficient method of achieving vascular access.<sup>55</sup> However, if HD is performed three times per week via AVF, this will repeatedly expose patients to the stress and pain of approximately 320 needle punctures/year. It is often necessary to make more than one attempt at cannulation to maintain an adequate blood flow.<sup>25</sup> It is necessary to use large needles to achieve the required rate of flow for dialysis, which can often lead to bruising and pain, especially in patients with new fistulae.<sup>55</sup>

It has been suggested in the literature that AVF cannulation is an easy and painless procedure.<sup>28</sup> However, it has been shown that repeated insertion of the AVF needles can cause considerable pain, both on and between dialysis sessions, with subsequent fear and anxiety.<sup>25</sup> Patients consider pain during needle insertion the most common problem regarding dialysis vascular access.<sup>25,67</sup> AVF-cannulation pain may adversely impact quality of life, and pain is cited as the primary reason for patients failing to tolerate dialysis via AVF.<sup>68</sup> Even though severe pain leading to regular avoidance of dialysis or abandonment of AVF is rare, over 10% of patients have experienced pain severe enough to require early cessation of HD at least once.<sup>55</sup>

There have been a number of published systematic reviews<sup>69–71</sup> on the impact of the different puncturing technique on the incidence of AVF-cannulation pain, all with equivocal results, showing various limitations, such as incomplete literature search<sup>69</sup> or even overall poor quality and substantial heterogeneity among studies that precluded pooling of outcomes.<sup>70</sup> Pain arising from AVF access was common and often multimodal in nature, frequently leading to avoidance or shortening of dialysis sessions and even abandonment of otherwise well-functioning AVF. Furthermore, pain is often a sign of underlying anatomical problems with AVF, and should always be investigated in the first instance.<sup>55</sup>

A considerable number of studies in this systematic review analyzed the prevalence and/or severity of headache. Bana et al first described headache during HD in 1972, and reported its prevalence as 70%.<sup>72</sup> Before 1988, the taxonomy

of headache was not uniform, and diagnostic criteria were rarely based on operational rules. In 1988, the IHS instituted a classification system that has become the standard for headache diagnosis and clinical research. The classification was endorsed by all the national headache societies represented in the IHS and also by the World Federation of Neurology.<sup>73</sup> The 1988 IHS criteria for headache related to HD consider that the headaches must begin during HD and terminate within 24 hours. However, it has been noted that some headaches cannot be classified.<sup>48</sup> The IHS revised the criteria for HDH in 2004, and described this condition as a headache that starts during an HD session and resolves within 72 hours after the session.<sup>74</sup> Our systematic review has shown the prevalence of headache, and particularly HDH, to be very high and among the most common problems in the HD population.

With regard to musculoskeletal pain, Braz and Duarte indicated that they excluded patients with previously confirmed rheumatologic disease or who said they had any osteoarticular manifestation before the HD treatment (episode of arthritis of unknown etiology, bursopathy, and diffuse bone pain, among others, not properly investigated or undiagnosed) to prevent these as potential confounding factors.<sup>40</sup> Such a statement was not present in other studies reporting general, limb, or musculoskeletal pain. Therefore, it is highly likely that high prevalence of limb and musculoskeletal pain in HD patients indicates comorbidities, and not such pain related to HD.

One of the strengths of this study is the inclusion of literature published in languages other than English and gray literature. In this way, we were able to locate multiple studies that were conducted outside Europe and North America. These studies indicated that pain is a considerable burden in developing countries as well.

Although this paper provides valuable data on the prevalence and severity of pain in HD patients, there were numerous limitations in the available evidence from primary studies. Data included in this systematic review indicate gaps that we still need to overcome in future literature on pain in HD patients. First, very few studies on the prevalence and severity of pain in HD patients were conducted in developing countries. Studies from those settings would be welcome for informing practice and research needs. Second, future studies need to pay particular attention to reporting, specifically for which period a patient is reporting pain. Several included studies did not report recall time for pain. Chronic pain was mostly defined as pain duration  $\geq 3$  months, but some studies did not define what they considered chronic pain, while some indicated that they measured chronic pain as pain lasting

at least 4 weeks.<sup>55</sup> Future studies should clearly indicate what they consider to be chronic pain and when exactly the pain was measured, ie, what the recall period expected of patients was (ie, current pain, pain in the last week, pain lasting  $\geq 3$  months).

Third, sample sizes need to be bigger. Half of the studies presented herein were small, with fewer than 100 patients included. The estimates of pain were sometimes based on median prevalence rates that may have been affected by the small sample size used, and should thus be interpreted with caution. Future studies should include a sufficient number of patients to gain a more representative sample. Fourth, validated pain-assessment tools should be used. The studies included in this review used various scales for pain assessment, which hinders comparability of pain intensity. While some studies used measures of pain intensity/severity to report average pain intensity, others reported the prevalence of different pain intensities in the analyzed sample. Future studies should all use the VAS for pain reporting, together with other pain-assessment scales. Additionally, studies should also report average pain, as well as percentage of patients experiencing different pain intensities. Furthermore, some of the included studies did not provide clear definitions of certain modalities of pain, such as cramps, making it difficult to judge whether these were indeed musculoskeletal cramps that are typical for HD patients.<sup>75,76</sup> Finally, the quality of the included studies was low to moderate. The authors of future studies should consult checklists for conducting and reporting trials, in order to improve the quality of available evidence.

The role of systematic reviews is to provide reliable actionable evidence, and also to point out where evidence is missing or when there are gaps in our research knowledge.<sup>77</sup> This systematic review provided a comprehensive overview of our current knowledge of the prevalence and severity of pain in HD patients, with actionable guidance for future studies on this topic. Based on the available evidence, prevalence and severity of pain varied widely between studies. It is thus necessary to explore factors associated with pain in HD patients to gain insight into the reasons behind such heterogeneity in pain prevalence and severity.

## Conclusion

The findings of this systematic review indicated a high prevalence of pain in HD patients, and thus pain in this population should be recognized as a considerable health concern. This review should encourage the nephrology community to promote pain management in HD patients as a clinical and research priority for improving quality of life

and pain-related disability. However, there are considerable gaps in the literature that future studies should address when devising a study protocol.

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