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ORIGINAL RESEARCH

Exploring Chronic Pain in Hemodialysis Patients: An Observational Study Based on the New IASP Classification for ICD-11

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ABSTRACT

***Introduction*:** Pain is one of the most frequently reported symptoms in hemodialyzed (HD) patients, with prevalence rates between 33% and 82%. Risk factors for chronic pain in HD patients are older age, long-lasting dialysis history, several concomitant diseases, malnutrition, and others. However, chronic pain assessment in HD patients is rarely performed by specialists in pain medicine, with relevant consequences in terms of diagnostic and treatment accuracy. Furthermore, no study has used the recently introduced International Association for the Study of Pain (IASP) pathophysiological classification.

***Methods*:** In this observational, cross-sectional study in a tertiary HD center in Northern Italy, we analyzed data regarding HD patients, evaluated for 5 months in 2021 by specialists in pain medicine and aimed to identify and characterize chronic pain according to the IASP definition and the last 2019 classification of chronic pain for ICD-11. Pain severity was evaluated by the pain severity score of the brief pain inventory tool.

***Results*:** Among 213 patients, 65 (31%) suffered from chronic pain. The average age was 73.1 years; 55.5% of the patients were male; 53.7% had diabetes, and 39.2% had arterial hypertension. Of the 54 patients subjected to an in-depth evaluation, data regarding 113 pain diagnoses were extracted, particularly related to osteoarthritis, obliterating arterial disease, and low back pain with or without radiculopathy. On the basis of these diagnoses, the pain classification according to the IASP pathophysiological definition highlighted a predominant nociceptive pain type (53.9% of all the diagnoses), followed by neuropathic (22.1%), mixed (22.1%), nociplastic (2.6%), and idiopathic (2.6%) pain. According to the IASP classification for ICD-11, the clinical diagnosis of chronic pain secondary to obliterating arterial disease and diabetes-related foot ulcers could not be assigned to any diagnostic category as a result of the lack of a specific item in the aforementioned classification.

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Conclusion: This study confirmed that chronic pain is a common, burdening issue in hemodialysis patients and that it is of a prevalent nociceptive nature. Our study highlights some limitations of the last IASP ICD-11 classification, especially the lack of specific items for some pain features that are very frequent in hemodialysis patients, and not only in that population. Finally, this study underlines the importance of mutual collaboration between pain physicians and nephrologists for the well-being of patients of high clinical complexity, such as those undergoing chronic hemodialysis.

Keywords: Chronic pain; End-stage renal disease; Hemodialysis; IASP classification; Observational studies

Key Summary Points

What was known: Pain is one of the most reported symptoms in hemodialysis (HD) patients, with prevalence rates between 33% and 82%. However, chronic pain assessment in HD patients is rarely performed by pain physicians, with relevant consequences in terms of classification, diagnosis, and treatment accuracy.

This study adds: Pain classification according to the IASP (International Association for the Study of Pain) pathophysiological definition highlighted a predominant nociceptive pain type, followed by neuropathic, mixed, nociplastic, and idiopathic pain classification. However, the last IASP classification for ICD-11 failed to classify, some pain features that are particularly relevant in HD patients.

Potential impact: Our study highlights some limitations of the last IASP ICD-11 classification, specifically the lack of specific items for some pain features that are very frequent in the population of HD patients. Moreover, this study highlights the importance of a mutual collaboration between pain physicians and nephrologists for these patients.

INTRODUCTION

End-stage renal disease (ESRD) is the final stage of chronic kidney disease, referring to individuals with an estimated glomerular filtration rate of less than 15 ml/min/1.73 m^2 body surface area or those requiring dialysis. The loss of kidney function in ESRD leads to fluid retention, electrolytes, and acid–base balance abnormalities, anemia, protein-energy malnutrition, and disturbances of bone and mineral metabolism that may be fatal in the absence of an appropriate kidney replacement therapy (KRT), such as kidney transplantation, which is the preferred treatment for eligible patients with ESRD, hemodialysis (HD), or peritoneal dialysis. The prevalence of ESRD is increasing worldwide, and HD is the most common choice of KRT [1]. Pain is one of the most reported symptoms in HD patients, with a prevalence between 33% and 82%, significantly higher than in the general population [2–5]. Risk factors for chronic pain (CP) in HD patients are older age, long-lasting dialysis history, several concomitant diseases, and malnutrition [6–10]. In most HD patients, pain onset is reported after the start of dialysis, and the severity ranges from moderate to severe, while in the general population, it is of mild to moderate intensity [11, 12]. Furthermore, pain worsens during HD treatment in 5–17% of patients [6, 7]. Pain severity and related depression represent the strongest risk factors for dropout of HD treatment [13]. Chronic pain in HD patients may arise from several factors related to uremic disease, like renal osteodystrophy, calciphylaxis, peripheral uremic neuropathy, and primary nephropathy (e.g., autosomal dominant polycystic kidney disease, ADPKD) [14]. Furthermore, chronic pain may be a consequence of the HD treatment, as in dialysis-related amyloidosis (DRA) that may lead to carpal tunnel syndrome (CTS), flexors tenosynovitis, or scapulohumeral periarthritis [15]. The presence of an arteriovenous fistula may cause painful ischemic neuropathy and increase the risk of osteomyelitis and discitis for bacterial translocation [16]. Also, diabetes is one of the most relevant risk factors for developing ESRD and is burdened by the development of painful neuropathy, diabetic foot, and peripheral vasculopathy [14]. Finally, HD patients may suffer from arthritis, musculoskeletal

disorders, persistent postoperative pain, visceral pain, headaches, fibromyalgia syndrome (FMS), and cancer-related pain [17, 18].

Until now, the characterization of chronic pain in HD patients was performed using different tools to assess pain type, prevalence, location, intensity, and interference with daily activities [4, 6, 7, 10, 11, 19–21]. Nevertheless, the use of a pathophysiological classification is mandatory to improve access to appropriate care for patients with CP. However, no study has used until now the recently introduced IASP pathophysiological classification. Moreover, pain assessment in HD patients has been mostly conducted by nephrologists so far. The aim of this observational study was to assess both the prevalence and the characterization of CP in a population of HD patients treated in a tertiary HD center in Italy with the collaboration of nephrologists and pain physicians and using the new 2019 IASP Classification of Chronic Pain for the ICD-11.

METHODS

Study Design

In this monocentric, observational, cross-sectional study we included patients of both sexes, aged ≥ 18 years, undergoing HD treatment for ESRD for at least 3 months at the time of enrollment. All the patients were treated in the AOUI (Azienda Ospedaliera Universitaria Integrata) HD Centre of Verona and have signed the informed consent for the investigation. All patients suffering from chronic pain, according to the IASP definition of "pain lasting at least 3 months," were selected [22]. In all of them, pain evaluation was performed by expert pain physicians who were external to the patient's care team. The primary aim was to assess the prevalence of chronic pain in the target population. The secondary aims were to apply both the IASP pathophysiological definitions and the new 2019 IASP Classification of Chronic Pain for the ICD-11 [22, 23], to classify the chronic pain diagnoses and to correlate the laboratory parameters related to secondary hyperparathyroidism and dialytic adequacy with the presence or absence of chronic pain in the whole analyzed population.

Data Collection

A specific clinical record form (CRF) was used to collect demographic, patient history, and clinical data during each HD session, including details on nephropathy and laboratory data on secondary hyperparathyroidism (calcium, phosphorus, parathyroid hormone—PTH), dialytic adequacy (urea, Kt/Veq according to the Daugirdas formula), and C-reactive protein [24]. These measurements referred to study entry and mean value during the previous year. Data on temporal, topographical, and descriptive features of pain, including onset, localization, description, and intensity, were collected. Pain intensity was assessed according to the pain severity score (PSS) extracted from the brief pain inventory (BPI) questionnaire [25]. The PSS is the average of the pain scores from 0 (no pain) to 10 (pain as intense as one can imagine) of questions 3–6 (intensity of the worst, mildest, average daily pain, and pain at the time of form filling, respectively). A pain intensity of 1–3 means mild pain, 4–6 moderate pain, and 7–10 severe pain. Instrumental investigations related to chronic pain were also evaluated for diagnostic purposes. At the end of each HD session, patients were physically evaluated to add more information regarding pain features.

Data Analysis

Quantitative variables were described using either mean and standard deviation (DS) as in the case of normal distribution or median and interquartile range (IQR) as in non-normal distribution. Frequencies and percentages have been used to describe categorical variables. The correlation between PSS and the considered clinical variables was evaluated with linear regression analyses and the Pearson correlation coefficient. The software R (version 3.4.4, R Foundation for Statistical

Computing) has been used to conduct the analyses. A p value < 0.05 was considered to be statistically significant.

Ethical Approval

All the study procedures were found to be in accordance with the Helsinki Declaration of 1975/83. The study was approved by the ethics committee of the Azienda Ospedaliera Universitaria Integrata of Verona (RED Register, 1751CESC). Informed consent was obtained from all patients included in the study.

RESULTS

From February 1 to June 30, 2021, 213 patients in HD treatment for ESRD were evaluated. Regarding chronic pain prevalence, among them, 65 (31%) reported chronic pain according to the IASP definition. In a deeper evaluation of pain, 11 patients were excluded from analysis for linguistic barrier or lack of consent. Therefore, the final evaluation was performed on 54 patients. The flowchart of the study population is given in Fig. 1. Demographics of the analyzed population are reported in Table 1. Details on nephropathy and HD in the analyzed population are reported in Table 2.

In the 54 analyzed patients, at the end of clinical evaluation, 113 clinical pain diagnoses were reported. These diagnoses are summarized in Table 3. On the basis of the clinical diagnoses, the pain classification according to the IASP pathophysiological definitions is summarized in Table 4.

Regarding pain assessment according to the 2019 IASP classification for ICD-11, 12 diagnoses of chronic primary pain were made, representing 10.6% of all diagnoses (Table 5). Following the same classification, 76 chronic secondary pain diagnoses were made, accounting for 67.2% of all diagnoses (Table 6). According to the new 2019 IASP classification for ICD-11, the clinical diagnoses of "chronic pain in lower extremity by obliterating arterial disease" (18 patients) and "chronic pain in diabetes-related foot ulcers (DRFU)" (7 patients) were impossible to assign for lack of a specific item and have been left unclassified. Regarding pain intensity, according to PSS, 13 patients (24.07%) reported mild pain, 33 patients (61.1%) reported moderate pain, and 8 patients (14.8%) reported severe pain. Finally, the laboratory data showed adequate dialysis (Kt/V > 1.2) and equal secondary hyperparathyroidism parameters in our HD patients with

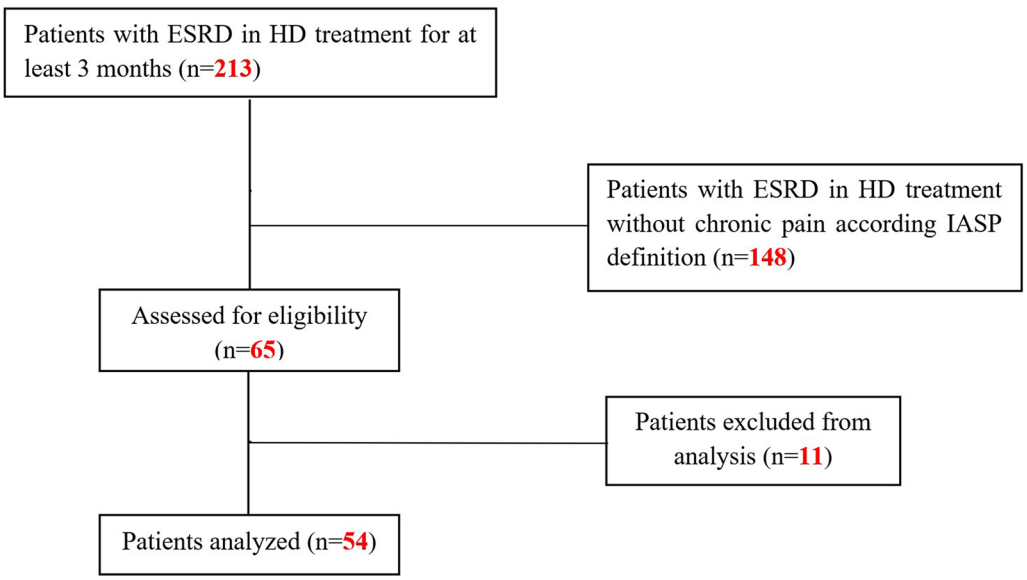

Fig. 1 Flow diagram of the study population

Table 1 Demographic characterization of the studied population

Assessed for evaluation	Overall $n = 54$
Age, years, mean (SD)	73.1 (10.2)
Sex, *n* (%)	
Female	24 (44.4)
Male	30 (55.5)
BMI, kg/m^2, median [IQR]	25.8 [8.8]
Smoke (previous or actual), *n* (%)	37 (68.5)
Alcohol (actual), *n* (%)	16 (29.6)
Comorbidities, median [IQR]	4.0 [2.0]
Reported comorbidities, *n* (%)	
Diabetes	29 (53.7)
Peripheral vascular disease	26 (48.1)
Cerebral vascular disease	14 (25.9)
Previous bone fractures	17 (31.4)
Arterial hypertension	32 (59.2)
Peripheral neuropathy	26 (48.1)
Arthritis	19 (35.1)
Malignancy	19 (35.1)

SD standard deviation, *BMI* body mass index, *IQR* interquartile range

Table 2 Details on nephropathy, dialysis, and related issues of the analyzed population

Assessed for evaluation	Overall $n = 54$
Nephropathy, *n* (%)	
Chronic kidney disease of unknown etiology	18 (33.3)
Diabetic kidney disease	15 (27.7)
Glomerulonephritis	9 (16.6)
Polycystic kidney disease	4 (7.4)
Congenital anomalies of the kidneys and of the urinary tract	2 (3.7)
Others	6 (11.1)
Dialysis features	
Kt/Veq, mean (SD)	1.2 (0.2)
Vintage hemodialysis, months, median (IQR)	46.8 (42.3)
RRT-HDF, *n* (%)	25 (45.5)

RRT renal replacement therapy, *HDF* hemodiafiltration, *Kt/Veq* assessment of delivered dialysis (Daugirdas formula)

and without CP. Therefore, comparing the 54 HD patients with CP to an equal number of HD patients without CP, no statistically significant difference was revealed for any of the parameters (Table 7). Considering the small sample size, no further analysis was conducted to investigate the correlations between laboratory data and severity of CP.

DISCUSSION

This monocentric, observational, cross-sectional study performed in a cohort of 213 Italian patients with ESRD undergoing HD showed a prevalence of chronic pain of 31%. While this prevalence is higher than that reported in the Italian general population, it is currently, to our knowledge, one of the lowest prevalence rates reported in the literature among HD patients, both in Italy and worldwide. In fact, according to the most recent data, 37–48% of Italian HD patients suffer from chronic pain, while in the HD population worldwide, data from a large systematic review highlighted a noticeably higher prevalence, with a mean estimated prevalence of 60%, and even of 92% in some studies [5, 6, 12]. The lower prevalence of chronic pain in our population may be due to several factors including the vintage of HD treatment (i.e., how many months/years a patient has been on dialysis), general and nephropathy-related comorbidities, the level of compliance to pharmacological and non-pharmacological therapies, and the efficacy of general care and HD treatment. However, previous studies aiming to establish the impact of different risk factors for chronic pain development in large HD populations proved to be too heterogeneous to allow any consistent conclusion [26].

Table 3 Chronic pain diagnoses in the studied population at the end of clinical evaluation

Chronic pain diagnoses	*n* = 113
Chronic pain from osteoarthritis	31
Hip (monolateral or bilateral)	6
Knee (monolateral or bilateral)	11
Shoulder (monolateral or bilateral)	8
Hand or foot (monolateral or bilateral)	5
Multiple joints	1
Pain in lower extremity by obliterating arterial disease	18
Low back pain without radiculopathy	9
Low back pain with radiculopathy	8
Painful tendinopathy	8
Pain in DRFU	7
Chronic post-amputation pain	4
Joint pain from rheumatologic disease	3
Myofascial pain syndromes	3
Chronic pain following bone fracture	3
FMS	3
Abdominal idiopathic pain	2
Chronic postsurgical pain	2
Amyloid painful polyneuropathy	2
Cervical pain without radiculopathy	1
CTS	1
Piriformis syndrome	1
PHN	1
Paresthesic meralgia	1
CRPS type I	1
Chronic pain following bone infraction	1
TTH	1
IBS	1
Neuropathic leg pain following poliomyelitis	1

Each patient may have multiple diagnoses

CRPS complex regional pain syndrome, *CTS* carpal tunnel syndrome, *DRFU* diabetes-related foot ulcers, *IBS* irritable bowel syndrome, *FMS* fibromyalgia syndrome, *PHN* postherpetic neuralgia, *TTH* tension type headache

Table 4 Pain classification according to IASP pathophysiological definitions

Chronic pain diagnosis	*n* = 113
Pain pathophysiology (diagnosis, %)	
Nociceptive	61 (53.9%)
Neuropathic	25 (22.1%)
Mixed	25 (22.1%)
Nociplastic	3 (2.6%)
Idiopathic	3 (2.6%)

From a pathophysiological point of view, the pain evaluation made by the expert pain physicians showed a moderately high prevalence of

Table 5 Chronic primary pain diagnoses in the studied population according to IASP classification for ICD-11

Chronic primary pain, *n* (%)	12 (10.6%)
Chronic widespread pain	3
CRPS (type I)	1
Chronic primary TTH	1
Chronic primary visceral pain	3
IBS	1
Chronic primary abdominal pain syndrome	2
Chronic primary musculoskeletal pain	4
Chronic primary cervical pain	1
Chronic primary thoracic pain	1
Chronic primary low back pain	2

Each patient may have multiple diagnoses

CRPS complex regional pain syndrome, *IBS* irritable bowel syndrome, *TTH* tension type headache

Table 6 Chronic secondary pain diagnoses in the studied population according to IASP classification for ICD-11

Chronic secondary pain, *n* (%)	**76 (67.2%)**
Chronic cancer-related pain	1
Chronic postsurgical pain or post-traumatic pain	6
Chronic pain after amputation	4
Chronic pain after herniotomy	1
Chronic pain after musculoskeletal injuries	1
Chronic neuropathic pain	15
Painful radiculopathy	10
Other specified and unspecified chronic peripheral neuropathic pain	1
Painful polyneuropathy	3
Postherpetic neuralgia	1
Chronic secondary musculoskeletal pain	54
Chronic musculoskeletal pain associated with osteoarthritis	31
Chronic pain associated with musculoskeletal injury	11
Chronic musculoskeletal pain associated with spondylosis	9
Chronic pain due to autoimmune and auto-inflammatory disorders	3

Each patient may have multiple diagnoses

chronic nociceptive pain due to osteoarthritis (31 diagnoses, 27.4%) followed by painful obliterating arterial disease (18 diagnoses, 15.9%) and low back pain with or without radiculopathy (17 diagnoses, 15%). Among HD-related pain syndromes, only three diagnoses of amyloid painful polyneuropathy and CTS were recorded (2.6%). When the most recent FMS diagnostic criteria were applied [27], three patients were diagnosed with fibromyalgia syndrome (2.6%), suggesting that FMS might be a significant burden also in HD patients [28].

To the best of our knowledge, this is the first study in the literature in which HD patients were evaluated by expert pain physicians using an accepted pain classification based on a pathophysiological approach. This may be a significant improvement in the process of pain diagnosis and related treatments in this particular population. Until now, not much attention was given to both the process of pain diagnosis and the criteria used to discriminate different types of pain in HD patients. In the available literature, pain diagnosis was often performed using different assessment tools such as the McGill Pain Questionnaire (MPQ) or the Leeds Assessment of Neuropathic Symptoms and Signs (LANNS) Scale. Furthermore, in previous studies, the algological examination was performed by nephrologists only, with some obvious limitations due to a lack of specific experience in pain diagnosis. As a result, in some observations, the type of pain was classified generically as osteoarticular, neuromuscular, peripheral vascular, musculoskeletal, or neuropathic without any reference to acknowledged classifications [5, 8, 10, 17, 18]. As an example, in some studies, phantom limb pain or CTS was not classified as neuropathic but was considered as a separate pain entity [19, 20], although their neuropathic nature is well accepted, allowing them to be classified as neuropathic pain syndromes for a long time [29]. Moreover, regarding low back pain the potential presence of a concomitant

Table 7 Laboratory data

	Chronic pain ($n = 54$)	Non-chronic pain ($n = 54$)	*P* value
Values at study entry			
Ca, mg/dL, mean (SD)	9.1 (0.7)	9.0 (0.7)	0.653
P, mg/dL, mean (SD)	5.1 (1.5)	5.3 (1.8)	0.606
CaxP, mean (SD)	45.8 (12.7)	47.3 (15.9)	0.585
PTH, pmol/L median [IQR]	27.2 [17.0]	29.0 [29.6]	0.857
Urea, mg/dL, mean (SD)	132.5 (41.2)	135.0 (38.6)	0.740
CRP, mg/L, median [IQR]	6.0 [9.5]	3.0 [4.5]	0.191
Kt/V, mean (SD)	1.2 (0.2)	1.2 (0.3)	0.468
Mean values during previous year			
Ca, mg/dL, mean (SD)	9.0 (0.5)	9.0 (0.6)	0.936
P, mg/dL, mean (SD)	5.1 (1.3)	5.3 (1.2)	0.512
CaxP, mean (SD)	45.8 (11.2)	47.6 (11.2)	0.417
PTH, pmol/L median [IQR]	26.1 [14.4]	27.2 [23.7]	0.363
Urea, mg/dL, mean (SD)	129.7 (30.4)	132.1 (30.2)	0.685
CRP, mg/L, median [IQR]	9.2 [17.1]	10.7 [28.9]	0.512
Kt/V, mean (SD)	1.2 (0.2)	1.2 (0.2)	0.437

Comparison between patients with and without chronic pain

radiculopathy was not investigated or recorded, thus neglecting an important feature with a significant impact on the therapeutic approach [5, 8, 10, 17, 19–21]. In our opinion, this non-standardized approach to pain diagnosis makes it difficult to estimate the actual prevalence of the different types of pain in this population. The obvious consequence is the risk of misdiagnosis and mistreatment of some pain syndromes.

When we applied the new 2019 IASP Classification of Chronic Pain for the ICD-11, 12 diagnoses (10.6%) were identified as chronic primary pain while 76 diagnoses (67.2%) referred to chronic secondary pain. As previously stated, 25 diagnoses (22.1%) were impossible to assign to one of the two aforementioned categories because of the lack of a specific item in the new classification. Notably, these clinical diagnoses (chronic pain in lower extremities by obliterating arterial disease and chronic pain in DRFU) are related to vascular diseases that are extremely common in HD patients as a result of underlying comorbidities such as arterial hypertension and diabetes mellitus [30]. Considering that the purpose of the ICD-11 classification of chronic pain is not only the epidemiological evaluation but also the analysis of different aspects of the disease (health management, research, clinical decision-making, reimbursement, and policy planning), the best of our efforts should be finalized to improve the new classification, as suggested by several authors, even if the actual evidence supports its use for better reliability compared to the previous ICD-10 classification [31–33].

Finally, in most of our HD patients affected by CP (41 patients, 75.9%), this was of moderate-severe intensity. This is a particularly high prevalence, consistent with the most up-to-date available literature, although this evidence must be considered with caution due to several limitations [16]. In fact, most of the reported studies were conducted in a small number of patients

and the definition of chronic pain is often not reported or not consistent with the most accepted definition. Moreover, the studies have used different scales for pain assessment, with limited comparability of pain intensity [12]. In our observation, however, the small sample size did not allow us to conduct further investigations regarding the impact of laboratory variables, HD efficacy, and severity of chronic pain.

Our observational study has some limitations, especially regarding the small number of patients compared to other similar studies reported in the literature. This limitation, as previously stated, did not allow us to evaluate other correlations such as those between pain intensity and comorbidities or type of nephropathy. The association between these parameters and pain in HD patients is well reported since the chronic kidney disease-mineral bone disorder (CKD-MBD) complication of uremia, in particular, affects both bones and arteries, with a risk of spontaneous fractures and ischemic disorders [10, 11]. However, these correlations will be the subject of future evaluations. In summary, this observational study confirmed that chronic pain is a relevant problem in HD patients. However, to refine the pain diagnosis and treatment, collaboration between pain physicians and nephrologists should be encouraged.

CONCLUSION

Our study confirms that chronic pain is frequent in hemodialysis patients and that it is generated by several factors. It also shows that the non-standardized approach to pain diagnosis used in many previous studies makes it difficult to estimate the actual prevalence of the different types of pain in this population. Without a pathophysiological-based classification, the risk of misdiagnosis and mistreatment of some pain syndromes is real. However, our study also highlights some limitations of the IASP ICD-11 classification, i.e., the lack of specific classes where to enter "chronic pain in the lower extremity by obliterating arterial disease" and "chronic pain in diabetes-related foot ulcers (DRFU)," two very frequent conditions in hemodialysis patients, but also in several other populations. Finally, this study underlines the importance of mutual collaboration between pain physicians and nephrologists for the well-being of hemodialyzed patients.

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Author Contributions. Vittorio Schweiger, Giovanni Gambaro and Martina Cacciapuoti were responsible for the study conception and design. Marta Nizzero and Vittorio Schweiger were responsible for patients' evaluation and clinical data collection. Salvatore Simari, Gianmarco Lombardi, Leonardo Gottin, Lisa Stefani and Alvise Martini were responsible for statistical analysis and data interpretation. Giustino Varrassi, Gabriele Finco and Enrico Polati were responsible for supervision or mentorship. Each author contributed with intellectual content during manuscript drafting or revision and agrees to be personally accountable for the individual's own contributions and to ensure that questions pertaining to the accuracy or integrity of any portion of the work, even one in which the author was not directly involved, are appropriately investigated and resolved, including with documentation in the literature if appropriate.

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Data Availability. Data used and analyzed for this study are available from the corresponding author upon reasonable request and after authorization of the local ethics committee.

Declarations

Conflict of Interest. Vittorio Schweiger, Martina Cacciapuoti, Marta Nizzero, Salvatore Simari, Gianmarco Lombardi, Leonardo Gottin, Lisa Stefani, Alvise Martini, Gabriele Finco, Enrico Polati and Giovanni Gambaro have nothing to disclose. Giustino Varrassi is an Editorial Board member of *Pain and Therapy*. Giustino Varrassi was not involved in the selection of peer reviewers for the manuscript nor any of the subsequent editorial decisions.

Ethical Approval. All the study procedures were found to be in accordance with the Helsinki Declaration of 1975/83. The study was approved by the ethics committee of the Azienda Ospedaliera Universitaria Integrata of Verona (RED Register, 1751CESC). Informed consent was obtained from all patients included in the study.

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