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SYSTEMATIC REVIEW

Dermatologic manifestations of hereditary hemochromatosis: A systematic review

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Abstract

Hereditary hemochromatosis (HH) is a genetic disorder leading to excessive iron absorption, impacting multiple organs, notably the skin, nails and mucosae. The objective of this study is to elucidate the dermatologic manifestations, associated symptoms, pathophysiology and management recommendations of HH. We searched five primary databases (PubMed, Embase, Cochrane Library, Scopus and Web of Science) up to April 2023. Non-English articles were included to minimize language bias. The studies were evaluated using Oxford Centre for Evidence-based Medicine standards, with adherence to PRISMA guidelines. Inaccessible articles were directly sourced from authors. Out of the initial 1582 publications from 1904 to 2023, 22 studies (19 in English, 2 in French and 1 in German) were selected. Most reports were from the USA, UK and France and were predominantly case reports, covering 148 patients with skin symptoms related to hereditary hemochromatosis. We collected data on the cutaneous findings and, when available, their histopathological features. The current study highlights the scope, variety and traits of dermatologic symptoms in hereditary hemochromatosis, pinpointing research gaps and areas for future exploration. Our review accentuates the diverse dermatological manifestations of hereditary hemochromatosis, notably hyperpigmentation, hypertrichosis and resistant pruritus, often linked to excessive iron deposition and subsequent impairment of skin cell function. We also found controversial evidence indicating that skin cancers seem to be associated with hereditary hemochromatosis. Porphyria cutanea tarda and hereditary hemochromatosis were frequently reported together. Given hereditary hemochromatosis's genetic nature, early identification in one individual can substantially guide familial care and preemptive interventions. Clinicians should prioritize hereditary hemochromatosis as a differential when patients present with specific dermatological symptoms, especially in sun-exposed regions. A rigorous assessment ensures accurate diagnosis, facilitating optimal management for both the patient and their family.

INTRODUCTION

Hereditary Hemochromatosis (herein HH) is an autosomal recessive disorder that affects approximately 1 in 200 individuals of European ancestry.[1,2] The pathophysiology of HH involves mutations in genes that regulate iron metabolism, leading to increased iron absorption and accumulation in various organs.[3] The most common form of HH is caused by mutations in the HFE gene,[4] but other genes, such as HJV and TFR2, have also been implicated.[5-7]

Increased iron deposition in the liver, heart, pancreas and skin leads to multiple manifestations.[4] Dermatologic

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manifestations of HH are common and may be one of the first signs of the disorder.[8] Skin findings include hyperpigmentation, particularly of the face, neck and hands, and other skin changes such as a bronze-like discoloration, hypertrichosis and xerosis.[9,10] Beyond these conventional signs, some evidence suggests that skin cancer may also be intricately linked to HH, expanding our understanding of its dermatologic implications.[11-13] HH is often diagnosed based on a combination of clinical features and laboratory testing, including serum ferritin levels, transferrin saturation and genetic testing.[14]

Current management recommendations for HH include phlebotomy to reduce iron overload and iron chelation therapy in cases where phlebotomy is contraindicated or ineffective.[4,9] Genetic counselling and screening of family members are also recommended due to the hereditary nature of the disorder.[9] Despite advances in understanding the pathophysiology and management of HH, there are still gaps in our knowledge regarding the disorder. For example, the mechanism by which iron deposition leads to hyperpigmentation and other skin changes is not entirely understood and is mainly attributed to melanin rather than iron deposition.[10,15,16] Additionally, more research is needed to improve the diagnosis and management of HH, particularly in populations with rare or novel mutations.[17]

To date, no comprehensive systematic review has evaluated the full spectrum of dermatologic manifestations of HH. This study aimed to illuminate the current understanding of HH with dermatologic manifestations up to April 2023.

MATERIALS AND METHODS

This systematic review endeavours to comprehensively examine the literature concerning the dermatologic manifestations of HH.[18]

Research question

To address our primary research question—'What insights does the current literature offer about the dermatologic manifestations of hemochromatosis, encompassing its symptoms, pathophysiology, risk factors, clinical signs, and current management recommendations?'—we employed a systematic review approach. This review conforms to the 'Preferred Reporting Items for Systematic Reviews and Meta-Analyses' (PRISMA) statement[19] in Table S2 of the supplementary file with PROSPERO registration ID: CRD42023460568.

TABLE 1 PICOS framework for this study.

Population	All ages and all races
Intervention/exposure	Hereditary hemochromatosis (HH)
Comparative/Control intervention	N/A
Outcome	Dermatologic manifestation (hair, skin, mucosa and nails)

Search strategy

The search strategy was developed using a combination of medical subject headings (MeSH) and keywords related to HH and dermatologic manifestations (Table 1). The search was conducted in five major electronic databases, including Web of Sciences, Scopus, PubMed, Embase and Cochrane Library, for articles published up to April 2023 (Table S1).

Study selection

After removing duplications, we screened the titles and abstracts of the identified studies to determine their eligibility for inclusion in the review. Two independent reviewers (HA and PJ) assessed the studies for inclusion/exclusion based on predetermined criteria. Any discrepancies in the inclusion/exclusion of studies were resolved through discussion and consensus.

1. The inclusion criteria for this systematic review were
   - Studies that described dermatologic manifestations of HH in human subjects.
   - Studies published in all languages.
2. The exclusion criteria for this systematic review were
   - Studies that focused solely on non-dermatologic manifestations of HH.
   - Studies that did not report dermatologic manifestations of HH.
   - Those that were not explicitly related to HH.
   - Duplicate publications, conference abstracts, animal studies, in vitro/in vivo studies and those with insufficient data.

Data extraction and synthesis

Two independent reviewers (HA and PJ) gathered essential details from each selected study using a standardized extraction form, and the following data were extracted: first author's name, country of the study's origin, year of publication, type of study, age, gender, total number of cases and the subset that displayed dermatologic manifestations, diagnostic confirmation method, description, location, and median duration of the cutaneous lesions, dermatologic histology findings, comorbidities, associated symptoms, patients' histories including habitual patterns, genetic predispositions, and any medications or treatments previously administered, treatment strategies and responsiveness of dermatologic symptoms to Iron Handling (IH) therapy.

Rating the quality of studies

The included studies were evaluated based on the Oxford Centre for Evidence-based Medicine—Levels of Evidence, wherein Level I corresponds to systematic reviews of

prospective cohort studies, Level II to ecological studies, Level III to non-consecutive cohort studies or those with a notably limited population, Level IV to case series or studies that utilize superseded reference standards, and Level V corresponds to the opinions of respected authorities and case reports. Authors collaboratively reviewed and unanimously agreed upon this classification.[20] Any discrepancies in the quality assessment between the two reviewers were resolved through discussion. The corresponding author was consulted to finalize the decision if a consensus was not reached.

RESULTS

The search strategy was designed to ensure the highest inclusivity, and the results were gathered from 1904 (the first available paper on the topic) up to April 2023. The primary search resulted in 1994 potentially relevant publications. After removing duplicates, 1582 studies were considered for the title and abstract screening, of which 1362 irrelevant articles were excluded, and 210 articles were included for full-text assessment. Finally, 22 studies met the inclusion criteria (Figure 1). During the screening process, we did not consider any language restrictions, and Google Translate also translated all related non-English papers to avoid language bias. Among the included studies, one was in German,[21] and two were in French.[22,23] In our research process, we encountered limitations in accessing the complete texts of 11 pertinent articles. To address this, we proactively reached out to the primary or corresponding authors in an attempt to obtain the full manuscripts. Notably, our proactive approach was successful in one such instance, allowing us to incorporate that specific article into our comprehensive study.[24]

Level of evidence for included studies

Upon applying the criteria set forth by the Oxford Centre for Evidence-based Medicine—Levels of Evidence in our methodology, a striking observation was made regarding the evidence quality of the encompassed studies. Remarkably, except for one cross-sectional study and two case series (level IV),[25] all other studies were case reports included in our review and were categorized under Level V. Such a uniform classification indicates a predominant presence of low-level evidence across the reviewed research (Table 2).

Characteristics of the included studies

Most of the included studies were from the USA (6/22), followed by the UK (4/22), France (3/22), Germany and Netherlands (2/22), and Belgium, Chile, Spain, Croatia and Denmark (1/22) (Figure 2a and Table 2). Studies were published from 1964 to 2022 (Figure 2b and Table 2). The majority of the included studies were case reports (19/22); the others were case series (2/22) and cross-sectional (1/22), as depicted in Figure 3b and Table 2.

A total of 148 patients with hereditary or idiopathic hemochromatosis were examined. In most of the included studies, the diagnosis of HH was confirmed using HFE gene analysis along with the clinical findings, high ferritin and iron indexes in serology, and, in some cases, skin or liver biopsy (Table 2).

The majority of the studied population were men (80.4%, 119/148), and the mean age of the total population was 55.88 years (Table 2 and Figure 3a).

Characteristics of the studied population

The most frequently reported comorbidities in HH patients were as follows: Diabetes mellitus (67.21%, 82/122), gonadal deficiency (49.18%, 60/122), heart disease (36.06%, 44/122), bone and joint disorders including osteoarthritis (32.78%, 40/122), hypothyroidism (12.29%, 15/122) and PCT (9.01%, 11/122) (Table S3).

Hepatomegaly (83.33%, 95/114), weight loss or cachexia (71.92%, 82/114), anorexia (71.05%, 81/114), abdominal pain (35.96%, 41/114) and malaise or fatigue (4.38%, 5/114) were the most common reported associated signs and symptoms, respectively (Table S3).

While data regarding alcohol consumption or smoking habits of the patients were not comprehensive, from the available information, a majority of the patients had a history of alcohol use (61.53%, 8/13). Regarding smoking, only 25% (1 out of 4) of the patients had a smoking history. Notably, alcohol consumption was more frequently reported among HH patients who were diagnosed with PCT. There was a family history of HH in several cases,[26,27] but no specific family history was found in several other HH patients.[21,23,24,28,29] Insulin, the oral contraceptive pill (OCP) and systemic or topical corticosteroids were the most reported drug history of these patients (Table S3).

More details regarding the comorbidities, associated signs and symptoms, and habitual, family and drug history of our studied population are available in Table S3.

Characteristics of the dermatologic findings in HH patients

The predominant dermatologic manifestation among HH patients was hyperpigmentation,[10,21,23,26,28,29,30] characterized by features such as hyperpigmented scars,[21] greyish skin pigmentation[23] and tanned skin.[30] These manifestations predominantly appeared on areas of the body exposed to light or presented as a generalized trait. The evidence concerning oral mucosa pigmentation remained inconclusive. One study noted buccal mucosa involvement in 18% of their cohort of 100 HH patients,[10] while a prospective

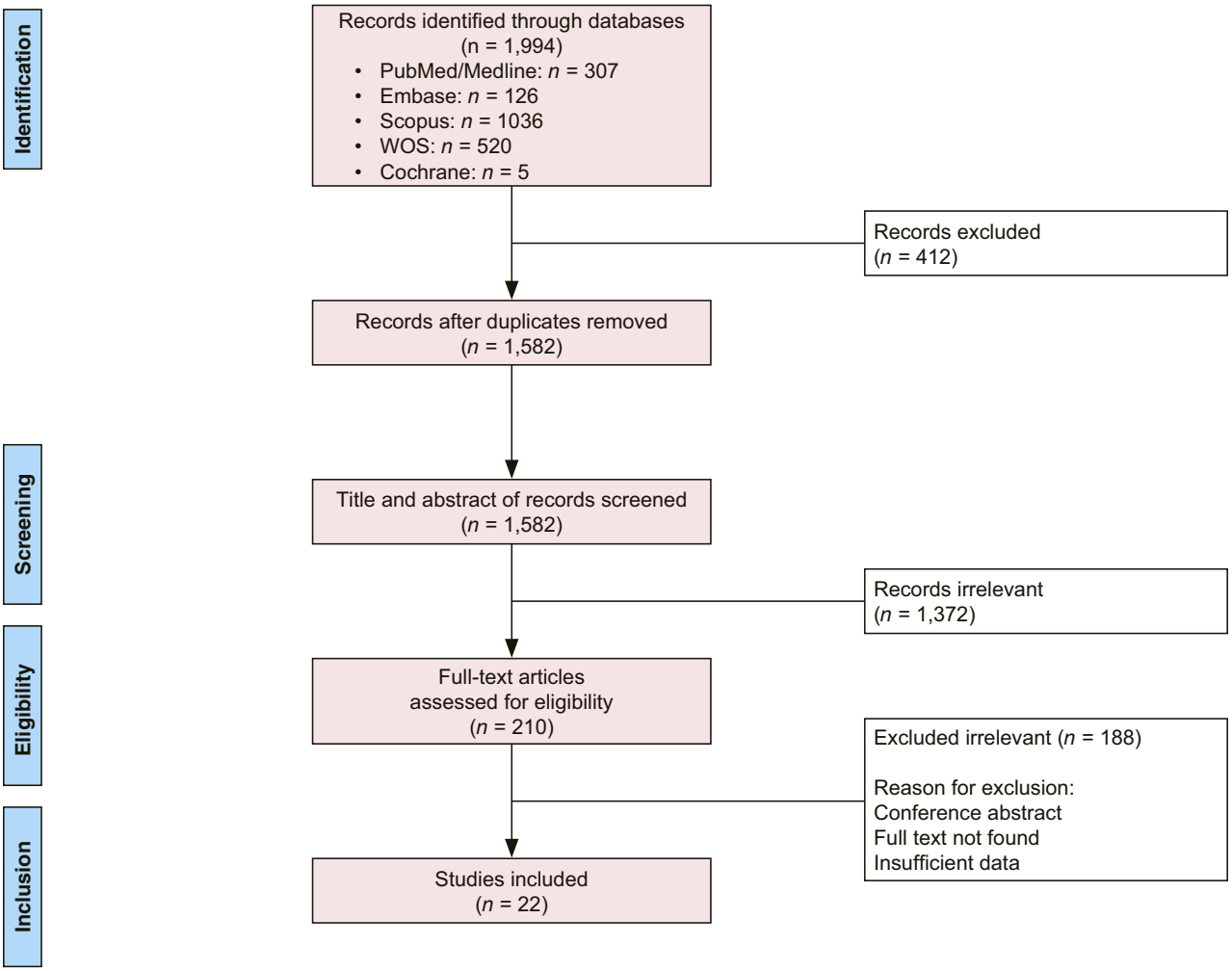

FIGURE 1 The PRISMA flow chart of study selection for inclusion in the systematic review.

cross-sectional study with 25 participants did not observe any oral pigmentation.[25]

Hypertrichosis on the face was documented[31]; concurrently, a potential concomitance with PCT was observed, resulting in fragile skin and non-pruritic blisters.[21,28,29,31,32,33,34] The latter also included milia,[21,28,31,32,33,34] which manifested with or without associated pain or a burning sensation. These conditions were typically observed on sun-exposed regions, particularly on the dorsal side of the hands. Nearly all the patients exhibiting these symptoms were diagnosed with PCT in conjunction with HH.

Skin atrophy and atrophic scars were also observed in several cases, particularly on the dorsal hands or anterior surfaces of the legs.[10,28,34]

A rare dermatologic manifestation, vitiligo, was documented in two HH cases.[35,36] These patients had an extended history of vitiligo, spanning over 25 years. Furthermore, one of these individuals was also diagnosed with PCT.[35] The vitiliginous patches manifested on sun-exposed body regions in one patient,[35] while the other experienced an onset on the hands that later progressed to the arms, neck and face.[36]

Alopecia manifested in various forms, such as scarring alopecia,[29] alopecia areata[24,27] and alopecia universalis.[27] In the study of 100 HH patients, 62% presented with partial hair loss, while 12% reported total hair loss. This condition more frequently affected the pubic region.[10] Additionally, intense generalized pruritus was observed in three cases,[37-39] with one individual experiencing it specifically on the anterior and posterior thorax.[37] In one instance, the pruritus was exacerbated by warm showers[37] and was antihistamine-resistant in another.[39]

Other less common dermatologic manifestations in HH patients included koilonychia in the thumb, index and middle finger[10]; an ichthyosis-like state on the dorsal forearm, wrist, foot and pretibial surface[10]; sclerotic, sometimes purplish lesions with slightly erythematous borders in light-exposed areas[22]; erythematous papulonodular lesions in various stages of healing on the dorsal hands[40]; progressive pigmented purpuric lesions on the legs[24]; and pigmented keratinous cysts (pigmented epidermal cysts) found on the neck and back.[21,41]

Several studies indicated a possible link between HH and skin cancers, specifically melanoma and basal cell carcinoma

TABLE 2 Characteristics of the included studies.

First author	Country	Year of publication	Type of study	Mean age	Male/ female	Total cases	Cases with dermatologic manifestations	Diagnosis confirmation method	Quality assessment
Perdrup et al.[36]	Denmark	1964	Case report	47	1M	1	1	Skin and liver biopsy	V
Leyden et al.[41]	USA	1972	Case report	64	1M	1	1	Serology	V
Chevrant-Breton et al.[10]	France	1977	Case series	54 in F, 46 in M	89M, 11F	100	100	The diagnosis was based on well-established clinical and laboratory criteria reported elsewhere[41]	IV
Nestler et al.[37]	USA	1983	Case report	66	1M	1	1	Serology, liver biopsy	V
Hamilton et al.[38]	UK	1985	Case report	70	1F	1	1	Serology, liver biopsy	V
Seymour et al.[26]	UK	1990	Case report	73	1F	1	1	Serology, a history of adult-onset diabetes mellitus, liver biopsy	V
Buysschaert et al.[23]	Belgium	1991	Case report	59	1F	1	1	Serology, liver biopsy	V
Syn et al.[29]	UK	2005	Case report	78	1F	1	1	Serology, HFE gene analysis, liver biopsy	V
de Geus et al.[33]	Netherlands	2006	Case report	56	1 M	1	1	Serology, HFE gene analysis	V
Kluger et al.[39]	France	2007	Case report	47	1F	1	1	Serology, HFE gene analysis	V
Young et al.[32]	USA	2007	Case report	41	1F	1	1	Serology, HFE gene analysis	V
Mogl et al.[35]	Germany	2008	Case report	68	1M	1	1	Serology, HFE gene analysis	V
Bovenschen et al.[28]	Netherlands	2009	Case report	27	1F	1	1	Serology, HFE gene analysis	V
Wolf et al.[30]	UK	2010	Case report	81	1F	1	1	Serology, HFE gene analysis	V
Sánchez-Pablo et al.[25]	Spain	2012	Prospective cross-sectional	52	20M, 5F	25	0	Serology, HFE gene analysis	IV
Tišma et al.[24]	Croatia	2012	Case report	56	1M	1	1	Clinical findings, serology, skin biopsy, HFE gene analysis	V
Wallaeys et al.[21]	Germany	2014	Case report	55	1F	1	1	Serology, HFE gene analysis	V
Trofymenko et al.[34]	USA	2017	Case report	34	1M	1	1	Serology, HFE gene analysis	V
Brunet et al.[22]	France	2018	Case report	59	1F	1	1	Serology, HFE gene analysis	V
Edwards et al.[40]	USA	2019	Case report	45	1M	1	1	Serology, HFE gene analysis	V
Larrondo et al.[31]	Chile	2020	Case report	56	1F	1	1	Serology, HFE gene analysis	V
Leung et al.[27]	USA	2022	Case series	48.5	2M, 2F	4	4	Serology, HFE gene analysis	IV

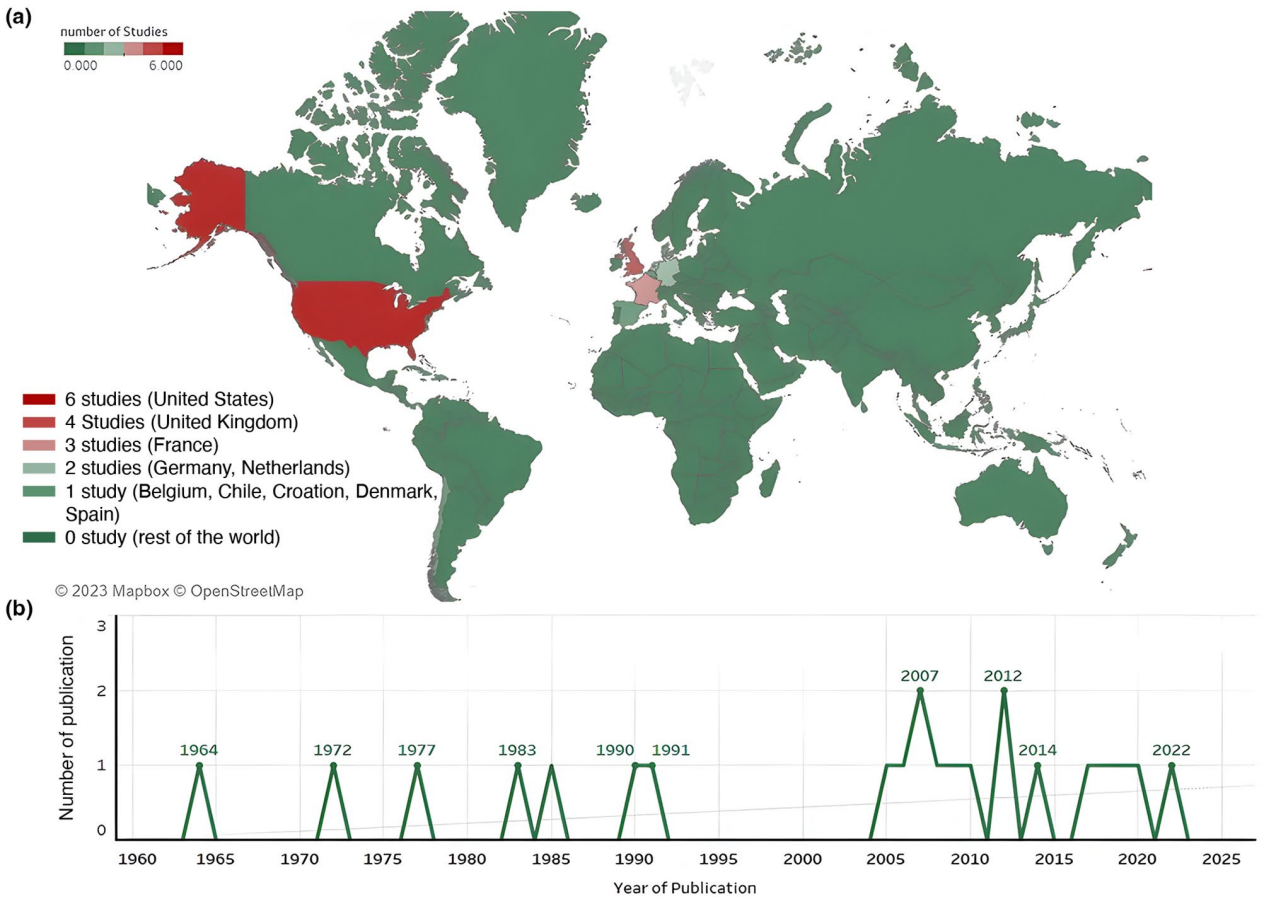

FIGURE 2 Distribution of countries (a) and timeline of the included studies (b).

(BCC).[11-13] However, these findings were not incorporated into our results and synthesis due to one of our exclusion criteria, which was the presence of insufficient data.

Predominant skin changes included the dorsal hands, face, arms and other sun-exposed body regions.

According to the available data, treatment protocols for HH patients predominantly incorporated phlebotomy/venesection, resulting in a clinically measurable reduction of the patients' cutaneous manifestations. However, in one study, nail signs were reported not to change following phlebotomy.[10] In several reports, blisters associated with concomitant PCT were successfully treated with a low-dose hydroxychloroquine administration with or without phlebotomy.[21,28,34] Combining immunotherapy (like diphenylcyclopropenone), corticosteroid use and phlebotomy for those exhibiting alopecia provided effective results, both as standalone treatments and in conjunction.[24,27,29]

The distribution of the lesions is shown in Figure 4, and for a detailed examination, skin biopsies were conducted in some instances. Comprehensive histopathologic findings from these biopsies are provided in Table S4. A summary of the more frequently reported clinical characteristics and dermatologic findings of our studied population with a calculated prevalence is available in Table 3.

DISCUSSION

Our investigation yielded 22 papers explaining the interplay between dermatology and hereditary hemochromatosis. A predominance of Level V evidence suggests a pressing need for more rigorous research.

One substantial finding was that hemochromatosis should be considered a crucial differential diagnosis in clinical practice for patients presenting with generalized symptoms such as hyperpigmentation and resistant pruritus. Less frequently, these patients might exhibit symptoms like alopecia and vitiligo, with a potential concomitance with PCT. In our reviewed studies, skin manifestations were the primary and the only complaint of the majority of HH cases,[21,22,24,27,28,29,31,32,34,36,37,38,39,41,42] highlighting the importance of a systematic approach by physicians in case of dermatologic presentations. We also emphasize the need for iron profile workup and consideration of hemochromatosis in patients presenting with general unexplained pruritus, alopecia areata, excessive skin pigmentation or unusual pigmentation in structures not being pigmented before, like keratinous cysts (epidermal cyst).[27,37,38,41]

The underlying mechanisms behind the pathophysiology of dermatological manifestations in HH patients remain elusive. Notably, skin hyperpigmentation is thought to arise

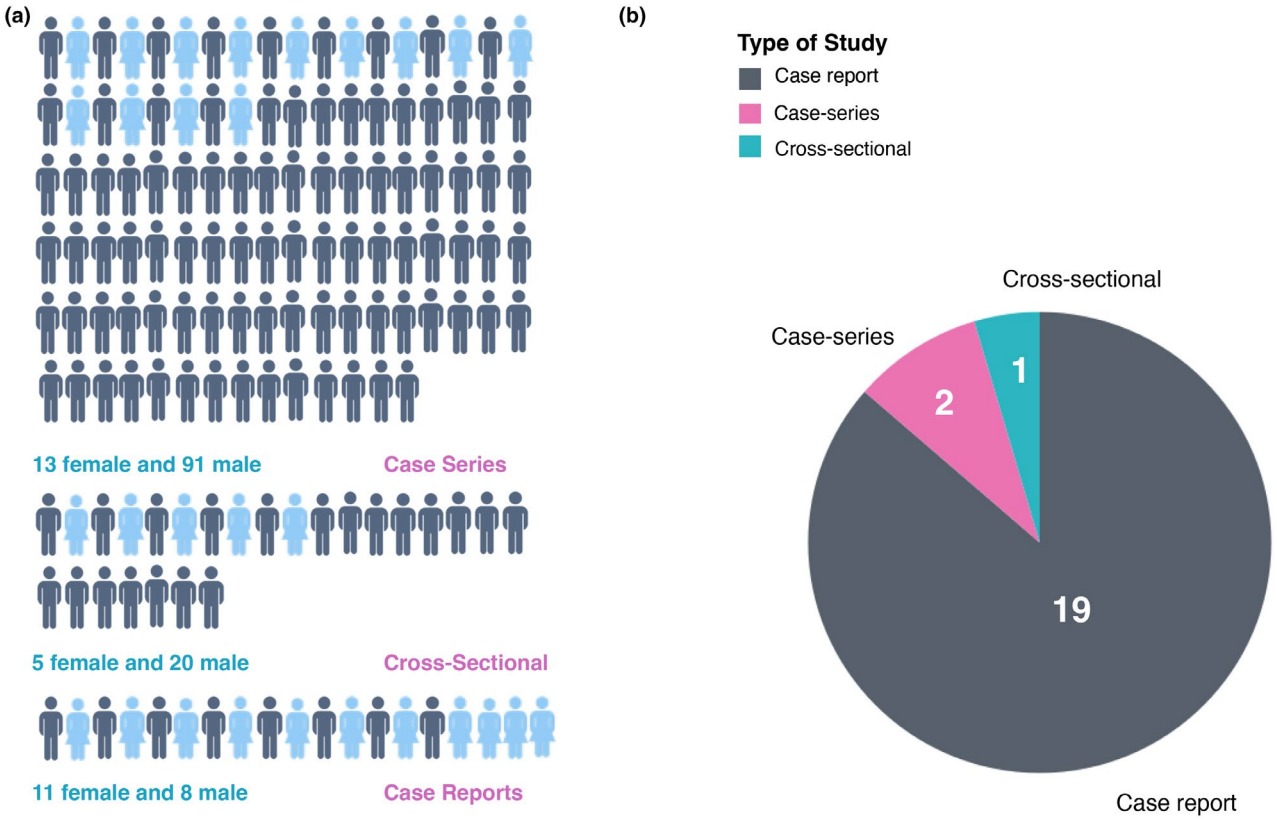

FIGURE 3 Description of the included studies based on their population (a) and methodology (b).

from melanin accumulation and iron deposits.[24,43] However, there is controversy regarding the role of iron deposits in hyperpigmentation. Since iron deposits in the epidermis of vitiligous patients are not able to neutralize the melanogenic defect, it seems that hyperpigmentation in HH patients may be exclusively attributable to melanin.[36,41] On the other hand, Chevrant-Breton et al. suggested siderosis in eccrine sweat glands as the specific histologic finding of HH. Also, they found no correlation between the clinical shade of hyperpigmentation and the degree of melanin or iron deposits in the skin.[10] Further studies are warranted to elucidate this association in depth.

Unexplained pruritus, resistant to common treatments, is the other skin manifestation in the context of HH. Pruritus is more commonly reported in iron deficiency.[44] However, there are two hypotheses regarding the mechanisms involving pruritus in HH: direct stimulation of C-class fibres by iron deposits of the skin and local release of histamine from tissue mast cells by stimulating iron deposits. Due to the ineffectiveness of antihistamine therapy in several cases, the first hypothesis is more probable.[37-39] Also, pruritus might be associated with HH complications such as hypothyroidism or cholestasis.[39] A comprehensive exploration, including screening for the patient's iron profile, should be applied to avoid missing either iron deficiency or HH in the context of pruritus complaints.

HH is frequently diagnosed between 40 and 60 years of age, with women presenting later due to physiologic iron loss during menstrual cycles and pregnancy.[30] Our study's mean age was congruent with this, at 55.88 years. However, HH should be considered in elderly patients with mildly deranged liver function tests and dermatologic manifestations, as reported by Hamilton et al. and Wolf et al.[30,38]

Additionally, there is an established connection between hepatic function and dermatological manifestations, with PCT frequently emerging in patients with severe hepatic conditions such as cirrhosis and hepatocellular carcinoma.[35] Given these observations, it becomes imperative for dermatologists to be apprised of this hepatic-dermatological connection, providing an avenue for timely interventions in potential hepatic anomalies.

The relationship between PCT and HH transcends anecdotal correlations, finding robust underpinnings both epidemiologically and pathophysiologically. An array of international studies have spotlighted a heightened prevalence of HH mutation carriers, both homo- and heterozygous, among sporadic PCT patients, including Australia,[45] USA,[46] UK,[47] Italy,[48] Germany[49,50] and the Netherlands.[51] A compelling meta-analysis further augments this association, revealing that individuals with the C282Y mutation in the HFE gene confront a staggering 48-fold increase in PCT susceptibility.[52] While the intricate mechanisms by which HFE mutations exacerbate PCT risk remain a topic of ongoing investigation, current hypotheses gravitate towards the roles of H63D and C282Y mutations in iron accumulation and uroporphyrinogen decarboxylase, an enzyme involved in the biosynthesis of haem, inactivity.[48]

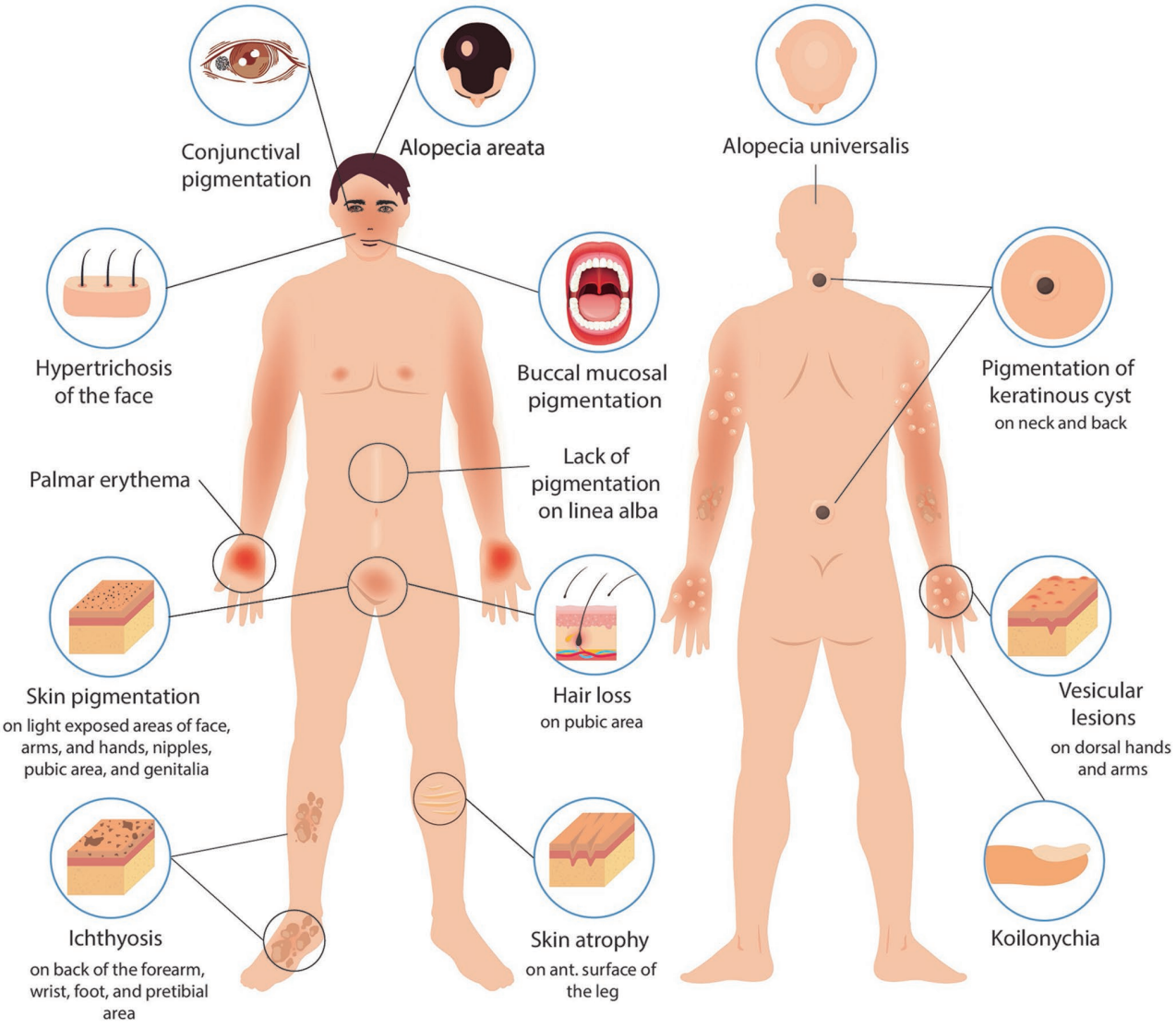

FIGURE 4 Illustration of dermatologic lesions in the hereditary hemochromatosis population in our review.

In a clinical milieu, PCT might serve as an early sentinel for underlying hemochromatosis.[28,34] A notable study indicated that 63% of patients co-diagnosed with PCT and hemochromatosis initially presented with PCT-associated symptoms, which subsequently unveiled the latent hemochromatosis.[53] This observation accentuates the need for proactive HH screening in PCT patients.

The relationship between HH and dermatological manifestations, especially skin cancers, remains debatable. X. Pan et al. found a 111% higher likelihood of BCC in HH patients (odds ratio 2.11; 95% CI, 1.288–3.450; $p = 0.005$). Moreover, HH patients with phlebotomy were more susceptible to NMSC (odds ratio 5.73; 95% CI, 1.293–25.367; $p = 0.015$).[13]

In contrast, Barry et al.'s study from Ireland, spanning 25 years, showed that 3.5% of HH patients had NMSC. However, their analysis had no significant link between BCC and HH (odds ratio for BCCs 1.90; 95% CI, 0.7–5.08; $p = 0.19$), despite Ireland's high HH prevalence rate.[11] A Danish study highlighted a significant melanoma risk among primary hemochromatosis patients with an SIR of 27.8 (95% CI, 3.1–100.3), underlining the melanoma vulnerability in these patients.[12]

From the nexus of data, it is evident that a sagacious understanding of familial histories, adept recognition of associated systemic symptomology and cognizance of potential co-morbid conditions are cardinal. For instance, the diagnostic implications of specific dermatologic signs, such as vitiligo, combined with familial patterns (as shown by Perdrup et al.[36]), could be instrumental. Concurrently, the preponderance of PCT in the dataset suggests heightened vigilance, mainly when observed with congruent systemic manifestations.

Still, our analysis is constrained by data limitations in some studies, emphasizing the need for more comprehensive research.

TABLE 3 Summary of more frequently reported clinical characteristics and dermatologic findings of the studied hereditary hemochromatosis patients.

	Characteristics	Number of studies	*n*/*N* (%)
Dermatologic findings	Hyperpigmentation (including scars, greyish skin, tanned skin)	9	105/108 (97.22)
	Alopecia (including alopecia areata and totalis)	5	81/107 (75.70)
	Nail changes (including koilonychia)	3	49/102 (48.03)
	Ichthyosis-like changes of skin	1	46/100 (46)
	Skin atrophy	2	43/101 (42.57)
	Mucosal pigmentation (including buccal, conjunctiva)	4	41/127 (32.28)
	Palmar Erythema	1	15/100 (15)
	Blistering and vesicular lesions	8	7/8 (87.5)
	Hypertrichosis	4	3/4 (75)
Comorbidities	Diabetes Mellitus	6	82/122 (67.21)
	Gonadal deficiency	1	60/122 (49.18)
	Heart disease	3	44/122 (36.06)
	Bone and joint disorders (including osteoarthritis)	4	40/122 (32.78)
	Hypothyroidism	6	15/122 (12.29)
	PCT	11	11/122 (9.01)
Associated signs and symptoms	Hepatomegaly	1	95/114 (83.33)
	Weight loss or cachexia	3	82/114 (71.92)
	Anorexia	2	81/114 (71.05)
	Abdominal pain	3	41/114 (35.96)
	Malaise or fatigue	5	5/114 (4.38)
Habitual history	Alcohol	13	8/13 (61.53)
	Smoking	4	1/4 (25)
Drug history	Insulin	3	NA[a]
	OCP	2	2/116 (1.72)
	Corticosteroid (systemic or topical)	1	3/116 (2.58)

Note: *N*: Total number of population in the included studies who had been evaluated for certain characteristics. *n*: Total number of patients with certain characteristics in the included studies.

Abbreviations: NA, not available; OCP, oral contraceptive pill; PCT, porphyria cutanea tarda.

[a]Due to undefined exact number of patients who were using insulin in one study (with 100 patients involved),[10] it could not be calculated any statistical data.

CONCLUSIONS

Our aggregated dataset presents a holistic overview of the interplay between dermatological manifestations and HH. While we have yet to pin down a standalone dermatological diagnostic protocol for HH, the insights gathered pave the way for future research. By honing diagnostic precision and developing tailored modalities, we remain optimistic about filling this diagnostic niche in the near future.

AUTHOR CONTRIBUTIONS

Concept and design: DM and HA. Acquisition, analysis, or interpretation of data: HA and PJ. Drafting of the manuscript: HA and PJ. Visuallization: HA and PJ. Critical revision of the manuscript for important intellectual content: DM, JC, HA, and PJ.

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FUNDING INFORMATION

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

All data were included in the manuscript and the supplementary file.

ETHICAL APPROVAL

This systematic review did not involve human participants, so ethical approval was not required.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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