Dermatology Practical & Conceptual

# Epidemiology and Clinical Characteristics of Harlequin Ichthyosis: A Systematic Review and Meta-Analysis of Case Reports

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**Key words:** Harlequin ichthyosis, Ichthyosis, Genetic skin disorders

**Citation:** Kurdi A, Alahmadi M, Alghamdi S, Albejawi L, Alghamdi L, Almutairi F, Alzahrani M, Almutairi L. Epidemiology and Clinical Characteristics of Harlequin Ichthyosis: A Systematic Review and Meta-Analysis of Case Reports. *Dermatol Pract Concept.* 2026;16(1):5911. DOI: https://doi.org/10.5826/dpc.1601a5911

**Accepted:** June 2, 2025; **Published:** January 2026



**Funding:** None.

**Competing Interests:** None.

**Authorship:** All authors have contributed significantly to this publication.

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## ABSTRACT

**Introduction:** Harlequin ichthyosis (HI) is considered one of the rarest and most severe congenital disorders, characterized by the development of thick, plate-like scales, ectropion, eclabium, and multi-system complications that mainly cause high neonatal mortality.

**Objectives:** This systematic review and meta-analysis aimed to comprehensively summarize all reported global case reports and series of harlequin ichthyosis, identifying common clinical presentations and geographic and genetic trends, and evaluating outcomes of different treatment approaches to inform better management strategies for this rare disease.

**Methods:** A comprehensive search across different databases using different predefined terms was conducted; only case reports and case series in English were included in this review.

**Results:** The review was conducted among 56 case studies and case series, including 68 cases that revealed that 64.7% had an unspecified genetic mutation, while 30.9 % carried an ABCA12 mutation. The clinical manifestations among the patients were severe, including thick scales, reported in 79.4%

of the patients, ectropion, reported in 80.9% of them, and eclabium, which was reported in 79.4% of the patients. Despite the supportive care received by the patients, the mortality rate was as high as 60.3%, with an average age at death of 47.19 days. Treatment response varied among the patients, with only 30.9% of them showing clinical improvement.

**Conclusion:** Our review highlights the significantly high morbidity and mortality rates associated with a diagnosis of HI, indicating the need for early diagnosis, genetic counseling, and improvement in the management strategies.

## Introduction

Harlequin ichthyosis (HI) is one of the rarest and most severe congenital disorders of keratinization, characterized by the development of thick, plate-like scales that cover the entire body and occur at birth, leading to severe epidermal barrier dysfunction, high incidence of infection, and dehydration [1,2]. This condition is mainly caused by the mutations in the ATP-binding cassette subfamily A member 12, abbreviated as the ABCA12 gene. This gene is important in the transport of lipids in the epidermis, causing defective skin barrier formation [3-5]. According to the literature, it is reported that the incidence of HI is estimated to be approximately one in 300,000 births worldwide, with a significantly higher incidence in regions with a high rate of consanguinity [6].

Neonates diagnosed with HI have several clinical phenotypic features, including the development of extropion, which is the eversion of the eyelids, eclabium, which is the eversion of the lips, and hypoplasia of the fingers and toes, with respiratory complications and a high risk of developing infection, sepsis, and dehydration [7]. The advances and development in neonatal intensive care (NICU) and the development and application of systematic retinoid therapy, including acitretin, have been associated with improvement in survival rates. However, the long-term treatment strategies remain challenging for these patients [8]. Despite those advancements, the survival rates in these patients remain poor, with a high rate of mortality mainly occurring in the first few weeks of life because of the development of associated complications, including respiratory distress, incidence of infections, and failure to thrive [9].

Diagnosis of HI is primarily clinical, based on characteristic dermatological manifestations, and can be confirmed through genetic testing [10]. Prenatal ultrasound findings such as excessive skin thickening and flexion contractures may provide early indications of the condition [11]. Histopathological examinations and skin biopsies can further support diagnosis in ambiguous cases [12]. Treatment is largely supportive, with an emphasis on intensive skin care, infection prevention, and nutritional support, alongside emerging targeted therapies aimed at improving epidermal function [12].

Given the rarity and severity of HI, a systematic review and meta-analysis are essential to synthesizing the available clinical data, identifying patterns in genetic mutations, clinical presentations, and treatment outcomes, and assessing the effectiveness of various therapeutic approaches.

## Objectives

The primary aim of this study is to consolidate and analyze published case reports and case series to provide a comprehensive global understanding of Harlequin Ichthyosis, specifically its epidemiological profile, clinical spectrum, genetic findings, and treatment outcomes. This consolidated analysis will serve as a valuable resource to guide early diagnosis, clinical decision-making, and the development of improved treatment protocols to enhance survival and quality of life in affected individuals.

## Methods

This systematic review and meta-analysis was conducted to assess the epidemiology of HI as well as its clinical features, genetic results, and outcomes of the treatment. It was devoid of any publication bias as the protocol was registered in the PROSPERO database (Registration ID: CRD42024628227). The study used the PRISMA criteria and the Population, Intervention, Comparison, Outcome, and Study Design (PICOS) framework to ensure a structured approach to collecting and analyzing data. The population of interest in the current review was the patients diagnosed with HI, while the main intervention component was to examine the epidemiological data, including incidence, associated complications, risk factors, clinical symptoms, genetic findings, and treatment outcomes. The primary outcomes measured were the prevalence and incidence rates of HI, demographic characteristics including age, sex, and geographic distribution, detailed clinical features, and prognosis, particularly survival rates and long-term complications.

Using a predefined search strategy, a comprehensive literature search was performed across multiple electronic databases, including MEDLINE (accessed via the PubMed interface), Google Scholar, Wiley Online Library, Web of

Science, and Embase. The search terms utilized included "Harlequin Ichthyosis" OR "Harlequin Fetus" OR "Congenital Ichthyosis" OR "Ichthyosis Congenita" in combination with "Case Report" OR "Case Series" OR "Clinical Case" OR "Case Study" to identify relevant clinical studies. Additionally, terms such as "Clinical Features" OR "Symptoms" OR "Clinical Presentation" OR "Phenotype" were used to extract data on the disease's manifestations. To obtain epidemiological data, the terms "Epidemiology" OR "Incidence" OR "Prevalence" OR "Demographics" were included. The search was limited to articles published in English, and only case reports or case series specifically involving patients diagnosed with HI were considered for inclusion. Studies that focused on other forms of ichthyosis, articles without case reports, and non-English publications were excluded.

Two independent reviewers screened all titles and abstracts to identify relevant studies, and full-text articles meeting the inclusion criteria were further assessed. Discrepancies in study selection were resolved through consensus or consultation with a third reviewer. Data extraction was carried out systematically, with information collected on study characteristics, patient demographics, clinical features, genetic mutations, diagnostic methods, treatment interventions, and reported outcomes. The extracted data were synthesized in a narrative format and, where applicable, pooled for meta-analysis. Statistical analyses were performed to determine prevalence and incidence rates, demographic distributions, and clinical outcome measures, ensuring a comprehensive synthesis of available evidence.

This methodology ensured a rigorous and systematic approach to evaluating HI, providing insights into its epidemiology, clinical spectrum, genetic findings, and treatment outcomes. The methodology is based on the need to consolidate global case-level evidence on harlequin ichthyosis to inform healthcare providers and researchers about its clinical burden and variations across populations.

## Results

The search across electronic databases yielded a total of 991 articles. Specifically, the search identified 117 studies through PubMed (indexing MEDLINE and other life science journals), 459 on Google Scholar, 282 via Wiley, 113 on Web of Science, and 19 studies on EBSCO. References were managed using Mendeley, and duplicate articles were removed, resulting in a total of 517 unique articles. Following the application of inclusion and exclusion criteria, 56 case studies and case series were selected for final inclusion (Figure 1).

HI has been reported in 56 case studies incldluing 68 cases across diverse geographic regions, with cases documented in Asia, Europe, the Americas, and Africa [1,8-11,13-63]. Most cases presented at birth, with an equal distribution between male and female neonates (50% for both sexes; sex was not reported in eight studies). A significant proportion of cases were associated with consanguinity (35.3% of the total 56 cases). However, when the analysis was restricted to only those studies that explicitly reported on parental relatedness (positive or negative history), the prevalence of consanguinity was found to be 45%. Additionally, a positive family history of genetic disorders was documented in 23.5% of cases. These findings were particularly prominent in populations from the Middle East and South Asia, suggesting a strong genetic component [22,34,53] (Table 1).

The pooled clinical characteristics of the 68 patients revealed diverse genetic mutations, with the majority (64.7%) having an unspecified genetic mutation, while 30.9% had an ABCA12 mutation. A rare compound heterozygous mutation in the ABCA12 gene was observed in 1.5% of cases, along with other uncommon findings such as transglutaminase 1 expression and combined ABCA12 and HRNR mutations, each occurring in 1.5% of patients. Regarding zygosity, 79.4% of cases lacked available data, but among the reported cases, 14.7% were homozygous, and 5.9% were heterozygous. In addition, patients' clinical features were prominent, with thick plate-like scales and eclabium reported in 79.4% of the patients and ectropion reported in 80.9 % of them. Hypoplasia of fingers or toes was identified in 36.8% of cases, while skin fissures or cracks were present in 75%. Moreover, respiratory distress was reported in more than half of the patients (51.5%), while 26.5 % of them had reports of infections, 35.3 % of the neonates had feeding difficulties, and 17.6 % had failure to thrive. In addition, sepsis was reported in 13.2 % of the patients, and dehydration was reported in 10.3% of them (Table 2).

Management and outcome measures among the 68 patients highlighted the predominant reliance on clinical examination for diagnosis in 86.4% of cases, with genetic testing and prenatal ultrasound each contributing to 18.2% of diagnoses. Histopathological examination (6.1%) and skin biopsy (10.6%) were less frequently utilized. Response to treatment varied, with 48.5% showing no improvement, while 30.9% demonstrated clinical benefit. Retinoid therapy was employed in 26.5% of cases, whereas 51.5% did not receive such treatment. In addition, supportive care measures were provided to almost two thirds of the neonates (66.2%), while surgical interventions were rarely performed, reported only in 5.9% of the cases. Mortality remained high at 60.3%, with a mean age at death of 47.19 days (Table 3). These results reflect the severity of HI and the limited effectiveness of current management strategies.

The methodological quality of the included case reports and case series was evaluated using the framework proposed by Murad, Sultan, Haffar, et al. (MMS) [74]. This assessment revealed variations in study rigor across different domains.

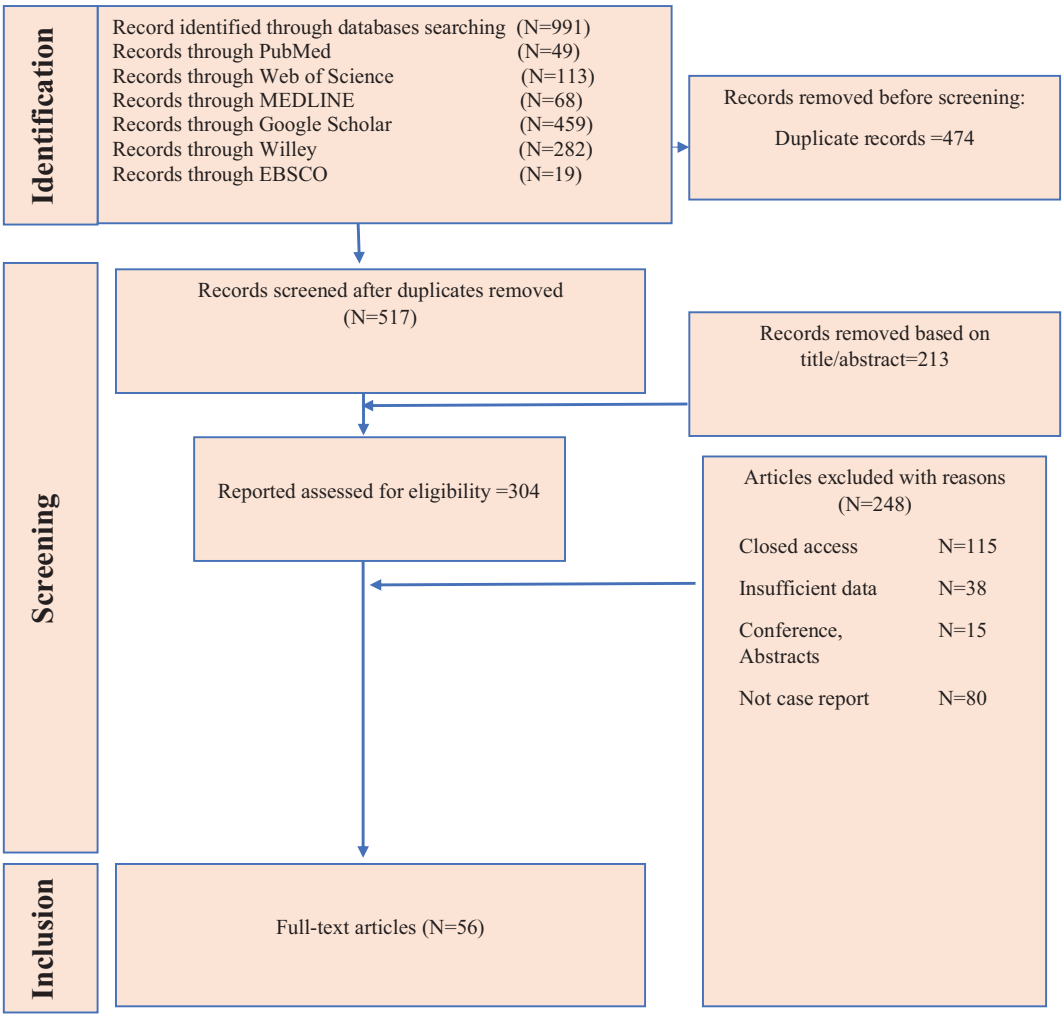


**Figure 1.** The PRISMA flow diagram showing the steps to choose the studies for systematic review.

Most studies demonstrated strong selection criteria and adequate ascertainment of exposure and outcomes, with nearly all cases reporting patient characteristics and clinical details comprehensively. However, challenges were noted in the causality domain, particularly in ruling out alternative explanations and assessing rechallenge phenomena, as these factors were not applicable in most clinical case reports. Reporting quality was generally high, with the majority of studies providing sufficient details to facilitate replication. However, some studies lacked comprehensive follow-up, limiting the ability to assess long-term outcomes. Despite these limitations, the overall methodological quality of the included studies was deemed acceptable for the purpose of this review (Table 4).

## Discussion

Harlequin ichthyosis (HI) is a rare, life-threatening congenital skin disorder with complex genetic origins and high neonatal mortality [7,64]. In this study, we aimed to systematically review and meta-analyze global case reports and series to consolidate the understanding of HI's clinical and genetic characteristics and treatment outcomes.

The findings of this study underscore the genetic heterogeneity of HI. While the majority of cases (64.7%) had an unspecified genetic mutation, the ABCA12 mutation was identified in 30.9% of patients. The ABCA12 gene is known to play a crucial role in lipid transport and skin barrier formation, and its mutations have been strongly implicated in the pathogenesis of HI [65,66]. Additionally, a small proportion of patients exhibited rare mutations such as compound heterozygous variants and transglutaminase 1 expression, indicating the potential involvement of alternative genetic pathways in HI pathogenesis [67].

Consanguinity was reported in 35.3% of the total cases reviewed. Notably, in the subset of studies where family history was explicitly documented, the prevalence of consanguinity increased to 45%. This finding aligns with previous reports suggesting a higher prevalence of autosomal recessive genetic disorders in populations with high rates of consanguineous marriages, particularly in the Middle East and South Asia [68,69]. Furthermore, a positive family history of

**Table 1. Study characteristics and patients' demographic and clinical characteristics**

| Study ID (Last name of first co-author, year of publication) | Study design (e.g. Case Report) | Country of origin | Number of patients included | Age at diagnosis (in years) | Sex | Ethnicity/ Race | Consanguinity | Family History of Harlequin Ichthyosis | Family History of Genetic Disorders | Birth Weight (in kilograms) | Gestational Age at Birth (in weeks) | Duration of Hospitalization (in days) | Mode of Delivery |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Jian , 2018 [25] | Case Report | China | 1 | 20-week gestation | NA | Chinese | No | No | No | Not applicable (pregnancy terminated). | 28 weeks (termination). | NA | Vaginal |
| Giacomina et al., 2016. [20] | Case Report | Brazil | 1 | 0 | Female | NA | No | No | No | 2650 | term | 3 | Cesarean |
| Zapałowicz et al., 2006 [59] | Case Report | Poland | 1 | 0 | Male | NA | No | No | No | 2900 | 37 | NA | Vaginal |
| Kün-Darbois et al., 2016.[27] | Case Report | France | 4 | 0 | Male and Female | NA | Yes | Yes | Yes | NA | 34-37 | NA | Vaginal |
| McKenzie et al., 2019 [32] | Case Report | United States | 2 | 0 | Male and Female | Hispanic | NA | No | No | NA | NA | NA | NA |
| Nikbina and Sayahi, 2022 [37]. | Case Report | Iran | 1 | 0 | Male | NA | No | No | No | 2700 | 36 | 5 | Cesarean |
| Habib et al., 2011. [22] | Case Report | Pakistan. | 1 | 0 | Male | NA | Yes | Yes | Yes | 2800 | 33 | 3 | Cesarean |
| Belengeanu et al., 2009. [13] | Case Report | Romania | 1 | 0 | Female | NA | No | No | No | 2430 | NA | 21 | Vaginal |
| Couto et al., 2019. [16] | Case Report | Brazil | 1 | 0 | Male | NA | No | No | No | 1815 | 34 | 15 | Vaginal |
| Baldo et al., 2021. [61] | Case Report and Literature Review. | Italy | 1 | 0 | Male | NA | No | No | No | NA | NA | NA | NA |
| Rajput et al., 2022. [9] | Case Report | Nepal | 1 | 0 | Female | NA | Yes | No | No | 3000 | 32 | NA | Vaginal |
| Washio et al., 2017. [10] | Case Report | Japan | 1 | 0 | Male | NA | No | No | No | 2650 | 37 | 73 | Vaginal |

*Table1 continues*

**Table 1. Study characteristics and patients' demographic and clinical characteristics.** *(continued)*

| Study ID (Last name of first co-author, year of publication) | Study design (e.g. Case Report) | Country of origin | Number of patients included | Age at diagnosis (in years) | Sex | Ethnicity/ Race | Consanguinity | Family History of Harlequin Ichthyosis | Family History of Genetic Disorders | Birth Weight (in kilograms) | Gestational Age at Birth (in weeks) | Duration of Hospitalization (in days) | Mode of Delivery |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Migowa et al., 2010. [33] | Case Report | Kenya | 1 | 0 | Male | African | No | No | No | 2300 | term | 8 | Vaginal |
| Londhe et al., 2022. [31] | Case Report | India | 1 | 0 | Female | NA | No | No | No | 2500 | 34 | 2 | Vaginal |
| Mithwani et al., 2014. [34] | Case Report | Saudi Arabia | 1 | 0 | Female | Saudi | Yes | No | No | 2400 | 37 | 240 | Vaginal |
| Beazley et al., 2011. [63] | Case Report | United Kingdom | 1 | 0 | Male | NA | No | No | No | NA | NA | 5 | NA |
| Bari and Najmi, 2020. [62] | Case Report | Pakistan. | 1 | 0 | Female | NA | Yes | No | No | NA | 36 | 3 | Cesarean |
| Castiglia et al., 2009. [14] | Case Report | Italy | 1 | 0 | Female | Italian | No | No | No | 890 | 31 | NA | Cesarean |
| Ogbe and Alarabi, 2020 [39]. | Case Report | Eritrea | 1 | 0 | Female | Eritrean | Yes | No | No | 2900 | 37 | 5 | Vaginal |
| Al-Dabbagh et al., 2022. [53] | Case Report | Syria | 1 | 0 | Male | Syrian | Yes | Yes | Yes | 2500 | 37 | 6 | Cesarean |
| Shrestha, 2022 [47] | Case Report and Literature Review. | Bangladesh | 1 | 0 | Female | NA | No | No | NA | 2500 | 36 | NA | Cesarean |
| Dahlstrom, 1995 [17] | Case Report | Australia | 1 | 0 | Female | Singaporean chinese | NA | NA | NA | 2415 | 35 | 3 | Vaginal |
| Choate, 1998 [15] | Case Report | USA | 1 | 2 | Male | NA | NA | NA | NA | NA | NA | 0 | NA |
| Hazukua, 2011 [24] | Case Report | Japan | 2 | 0 | Male | Japanese | No | NA | NA | 3126 | 37 | NA | Vaginal |
| Hazukua, 2011 [24] | Case Report | Japan | 2 | 0 | Female | Japanese | NA | NA | NA | 2566 | 38 | NA | Cesarean |
| Shahada, 2022 [46] | Case Report | Saudi Arabia | 1 | 0 | Male | Afghani | Yes | Yes | NA | 1600 | 39 | NA | Vaginal |
| Reyna-Villasmil, 2023 [44] | Case Report | Venezuela | 1 | 0 | Male | NA | Yes | No | No | 1300 | 30 | NA | Uterine evacuation |

| | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Lainingwala, 2023 [1] | Case Report | India | 1 | 0 | NA | NA | Yes | No | No | 1800 | 34 | NA | Vaginal |
| Tahir, 2024 [51] | Case Report | Pakistan | 1 | 0 | Female | NA | Yes | No | No | 1800 | 36 | 2 | Vaginal |
| LIANG, 2019 [28] | Case Report | China | 2 | 0 | Female | NA | No | No | No | 2000 | 31 | 2 | NA |
| LIANG, 2019 [28] | Case Report | China | 2 | 0 | NA | NA | No | No | No | NA | 24 | 0 | NA |
| Liu, 2021 [29] | Case Report | China | 1 | 0 | Male | Chinese | NA | No | No | 1990 | 23 | 0 | Vaginal |
| Tran, 2023 [52] | Case Report | Vietnam | 1 | 0 | Male | NA | NA | Yes | No | 2200 | 32 | 5 | NA |
| Gunes, 2003 [21] | Case Report | Turkey | 1 | 0 | Female | NA | Yes | No | No | 2800 | 37 | 21 | Cesarean |
| Olney, 1993 [38] | Case Report | USA | 2 | 0 | NA | Navajo | No | Yes | No | NA | NA | NA | NA |
| Olney, 1993 [38] | Case Report | USA | 0 | NA | Navajo | No | Yes | No | NA | NA | 2 | NA | |
| Ukkali, 2015 [55] | Case Report | Vijayapura | 1 | 0 | Female | NA | Yes | No | No | 2500 | 37 | 1 | NA |
| Paria, 2015 [40] | Case Report | India | 1 | 0 | Female | NA | Yes | Yes | No | 2570 | NA | NA | Vaginal |
| Verma, 2019 [57] | Case Series | India | 7 | 0 | Female | NA | NA | NA | NA | 2100 | 28 | 5 | Cesarean |
| Verma, 2019 [57] | Case Series | India | 7 | 0 | Female | NA | Yes | No | No | 1800 | 34 | 0 | Vaginal |
| Verma, 2019 [57] | Case Series | India | 7 | 0 | Female | NA | No | Yes | No | 2100 | NA | 0 | Vaginal |
| Verma, 2019 [57] | Case Series | India | 7 | 0 | Female | NA | Yes | No | No | 1900 | 33 | 1 | Vaginal |
| Verma, 2019 [57] | Case Series | India | 7 | 0 | Female | NA | No | No | No | 1500 | 35 | 1 | Vaginal |
| Verma, 2019 [57] | Case Series | India | 7 | 0 | Male | NA | Yes | No | No | 2300 | 33 | NA | Vaginal |
| Verma, 2019 [57] | Case Series | India | 7 | 0 | Male | NA | No | Yes | No | 1400 | NA | NA | Vaginal |
| Jilumudi, 2012 [26] | Case Report | India | 1 | 0 | Female | NA | NA | NA | NA | NA | 39 | NA | NA |
| Salehin, 2013 [54] | Case Report | Iran | 1 | 0 | Female | NA | Yes | No | No | 2100 | 30 | 0 | Vaginal |
| Ugezu, 2017 [54] | Case Report | Ireland | 1 | 0 | Female | NA | NA | NA | NA | 3140 | 35 | 11 | Cesarean |
| Parikh, 2016 [41] | Case Report | Pakistan | 1 | 0 | Male | Pakistan | Yes | Yes | Yes | NA | 33 | 48 | NA |

*Table1 continues*

Table 1. Study characteristics and patients' demographic and clinical characteristics. *(continued)*

| Study ID (Last name of first co-author, year of publication) | Study design (e.g. Case Report) | Country of origin | Number of patients included | Age at diagnosis (in years) | Sex | Ethnicity/ Race | Consanguinity | Family History of Harlequin Ichthyosis | Family History of Genetic Disorders | Birth Weight (in kilograms) | Gestational Age at Birth (in weeks) | Duration of Hospitalization (in days) | Mode of Delivery |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Liu, 2023 [30] | Case Report and Literature Review. | China | 1 | 0 | Male | NA | NA | No | No | NA | 30 | NA | Vaginal |
| Montalván-Suárez, 2019 [35] | Case Report and Literature Review. | Ecuador | 1 | 4 | Male | Ecuadorian | No | No | NA | NA | 28 | 30 | NA |
| Moreau, 1999 [36] | Case Report | France | 1 | 0 | Female | NA | NA | No | No | 2850 | 40 | 0 | Vaginal |
| Vijayakumari, 2020 [58] | Case Report | India | 1 | 0 | Female | NA | Yes | Yes | NA | NA | 32 | 0 | Vaginal |
| Pet, 2016 [42] | Case Report | Pakistan | 1 | 0 | Female | NA | No | NA | NA | NA | NA | 42 | NA |
| Devnani, 2019 [18] | Case Report | Pakistan. | 1 | 0 | Male | NA | Yes | No | NA | 2900 | 36 | 11 | Cesarean |
| Zhou, 2021 [11] | Case Report and Literature Review. | China | 1 | 0 | NA | NA | NA | No | No | NA | NA | NA | NA |
| Sanhal, 2013 [45] | Case Report | Turkey | 1 | 0 | Male | NA | Yes | Yes | NA | 2130 | 32 | 20 | Cesarean |
| Rajagopal, 2015 [43] | Case Report | India | 1 | 0 | Male | NA | NA | NA | NA | 1750 | 34 | 5 | Vaginal |
| Fatima, 2014 [19] | Case Report | Pakistan | 1 | 0 | Male | NA | Yes | Yes | NA | 2800 | 37 | 7 | Cesarean |

| | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Bahashwan, 2024 [8] | Case Report and Literature Review. | Saudi Arabia | 1 | 0 | Male | NA | No | No | No | 2200 | 33 | 30 | Vaginal |
| Vergotine, 2013 [56] | Case Report | USA | 1 | 0 | Male | NA | NA | NA | NA | NA | NA | NA | NA |
| Arias-Pérez, 2021 [60] | Case Report | Colombia | 1 | 0 | Male | NA | NA | No | No | NA | NA | 30 | NA |
| Suresh, 2004 [49] | Case Report | India | 1 | 0 | Male | NA | NA | NA | NA | 1700 | 37 | 3 | NA |
| Suresh, 2004 [49] | Case Report | India | 1 | 0 | NA | NA | NA | NA | NA | NA | NA | 1 | NA |
| Suresh, 2004 [49] | Case Report | India | 1 | 0 | NA | NA | NA | Yes | NA | NA | 27 | 0 | Vaginal |
| SUZUMORI, 1991 [50] | Case Report | Japan | 2 | 0 | Male | Japanese | No | Yes | NA | NA | NA | 14 | NA |
| Shruthi, 2017 [48] | Case Report | India | 1 | 0 | Female | NA | Yes | NA | NA | 1900 | 33 | 3 | Cesarean |
| Harvey, 2010 [23] | Case Report | USA | 1 | 0 | Male | NA | No | No | No | 2580 | 34 | 105 | Cesarean |

**Table 2. Pooled clinical characteristics of the patients (N=68 patients).**

| | | No. of cases | Percent of cases |
|---|---|---|---|
| Type of genetic mutation | NA | 44 | 64.7% |
| | ABCA12 mutation | 21 | 30.9% |
| | Compound heterozygote for mutations c.1552G>T (p. Glu518Ter) and c.859C>T (p. Arg287Ter) in the ABCA12 gene. | 1 | 1.5% |
| | transglutami0se 1 expression | 1 | 1.5% |
| | ABCA12 and HRNR | 1 | 1.5% |
| Zygosity | NA | 54 | 79.4% |
| | Heterozygous | 4 | 5.9% |
| | Homozygous | 10 | 14.7% |
| Presence of thick plate-like scales | NA | 14 | 20.6% |
| | No | 0 | 0.0% |
| | Yes | 54 | 79.4% |
| Ectropion (eversion of eyelid) | NA | 11 | 16.2% |
| | No | 2 | 2.9% |
| | Yes | 55 | 80.9% |
| Eclabium (eversion of lips) | NA | 13 | 19.1% |
| | No | 1 | 1.5% |
| | Yes | 54 | 79.4% |
| Hypoplasia of fingers or toes | NA | 22 | 32.4% |
| | No | 21 | 30.9% |
| | Yes | 25 | 36.8% |
| Skin fissures or cracks | NA | 14 | 20.6% |
| | No | 3 | 4.4% |
| | Yes | 51 | 75.0% |
| Respiratory issues | NA | 21 | 30.9% |
| | No | 12 | 17.6% |
| | Yes | 35 | 51.5% |
| Infections | NA | 25 | 36.8% |
| | No | 25 | 36.8% |
| | Yes | 18 | 26.5% |
| Feeding difficulties | NA | 23 | 33.8% |
| | No | 21 | 30.9% |
| | Yes | 24 | 35.3% |
| Failure to thrive | NA | 28 | 41.2% |
| | No | 28 | 41.2% |
| | Yes | 12 | 17.6% |
| Sepsis | NA | 30 | 44.1% |
| | No | 29 | 42.6% |
| | Yes | 9 | 13.2% |
| Dehydration | NA | 36 | 52.9% |
| | No | 25 | 36.8% |
| | Yes | 7 | 10.3% |

genetic disorders was documented in 23.5% of cases, providing further support for the hereditary nature of HI [7].

The clinical manifestations of HI are severe and life-threatening. The majority of patients (79.4%) exhibited thick plate-like scales, which is a hallmark of the disorder [53]. Ectropion and eclabium were also common findings, occurring in 80.9% and 79.4% of cases, respectively. These features contribute to significant morbidity, particularly due

**Table 3. Pooled management and outcomes measures among 68 patients.**

| | | No. of cases | Percent of cases |
|---|---|---|---|
| Diagnostic method | Clinical examination | 57 | 86.4% |
| | Genetic testing | 12 | 18.2% |
| | Prenatal ultrasound | 12 | 18.2% |
| | Histopathological examination | 4 | 6.1% |
| | Skin biopsy | 7 | 10.6% |
| Response to treatment | NA/Not treated | 14 | 20.6% |
| | No | 33 | 48.5% |
| | Yes | 21 | 30.9% |
| Use of retinoids | NA | 15 | 22.1% |
| | No | 35 | 51.5% |
| | Yes | 18 | 26.5% |
| Supportive care measures | NA | 9 | 13.2% |
| | No | 14 | 20.6% |
| | Yes | 45 | 66.2% |
| Surgical interventions | NA | 8 | 11.8% |
| | No | 56 | 82.4% |
| | Yes | 4 | 5.9% |
| Survival status | NA | 4 | 5.9% |
| | Deceased | 41 | 60.3% |
| | Alive | 18 | 26.5% |
| | Discharged | 5 | 7.4% |
| Age at death (day) | Mean (SD) | 47.19 (277.69) | |
| Evidence of clinical improvement | NA | 6 | 8.8% |
| | No | 41 | 60.3% |
| | Yes | 21 | 30.9% |

to impaired barrier function, dehydration, and increased susceptibility to infections [1,70].

Respiratory complications were noted in 51.5% of cases, which can be attributed to restrictive lung disease secondary to skin rigidity and impaired chest expansion. Previous literature has described similar respiratory distress in neonates with HI, necessitating ventilatory support in many cases [66]. Additionally, sepsis was observed in 13.2% of patients, highlighting the high risk of systemic infections due to compromised skin integrity and immune dysregulation [12]. Feeding difficulties and failure to thrive were also significant concerns, affecting 35.3% and 17.6% of patients, respectively, emphasizing the need for specialized nutritional support in these infants [12].

The diagnosis of HI was primarily based on clinical examination (86.4%), with genetic testing and prenatal ultrasound each contributing to 18.2% of cases. The reliance on clinical examination underscores the importance of early recognition and prompt intervention. However, the role of genetic testing in confirming the diagnosis and guiding genetic counseling cannot be overlooked [7,71].

Therapeutically, the response to treatment varied widely. Retinoid therapy, which has been shown to improve epidermal differentiation and reduce hyperkeratosis [72], was used in 26.5% of cases. Although systemic retinoids have demonstrated efficacy in improving survival and skin condition [72], concerns regarding their adverse effects and accessibility may limit widespread use. Supportive care measures were implemented in 66.2% of cases, focusing on hydration, infection control, and nutritional support, which are essential for improving survival [73].

Despite advancements in management, the prognosis remains poor, with a mortality rate of 60.3%. The mean age at death was 47.19 days, reflecting the severity of neonatal complications associated with HI. However, 26.5% of patients survived, and 7.4% were discharged, suggesting that with early diagnosis and aggressive multidisciplinary care, survival rates may improve. Notably, clinical improvement was observed in 30.9% of cases, reinforcing the potential benefit of intensive supportive management combined with targeted therapies [73].

This review highlights the urgent need for standardized diagnostic and treatment protocols and expanded access to genetic testing in at-risk populations. The inclusion of data from diverse geographical regions enhances the

**Table 4. Methodological quality assessment of case reports and case series based on the framework proposed by Murad, Sultan, Haffar, and Bazerbachi [74].**

| Reference | Selection | Ascertainment | | Causality | | Reporting | | |
|---|---|---|---|---|---|---|---|---|
| | Leading Explanatory Questions | | | | | | | |
| | Q. 1 | Q. 2 | Q. 3 | Q. 4 | Q. 5 | Q. 6 | Q. 7 | Q. 8 |
| Jian et al., 2018 [25] | Yes | Yes | Yes | Yes | N/A | N/A | No | Yes |
| Al-Dabbagh et al. 2022 [53] | Yes | Yes | Yes | Yes | N/A | N/A | No | Yes |
| Londhe et al., 2022 [31] | Yes | Yes | Yes | Yes | N/A | N/A | No | Yes |
| Zapałowicz et al., 2006 [59] | Yes | Yes | Yes | Yes | N/A | N/A | Yes | Yes |
| W & Alarabi et al., 2020 [39] | Yes | Yes | Yes | Yes | N/A | N/A | No | Yes |
| Couto et al., 2019 [16] | Yes | Yes | Yes | Yes | N/A | N/A | Yes | Yes |
| Giacomin et al., 2014 [20] | Yes | Yes | Yes | No | N/A | N/A | No | Yes |
| Habib et al., 2011 [22] | Yes | Yes | Yes | No | N/A | N/A | No | Yes |
| Bari et al., 2020 [62] | Yes | Yes | Yes | No | N/A | N/A | No | Yes |
| Washio et al., 2017 [10] | No | Yes | Yes | Yes | N/A | N/A | No | Yes |
| Kün-Darbois et al., 2015 [27] | No | Yes | Yes | Yes | N/A | N/A | Yes | Yes |
| Beazley et al., 2011 [63] | Yes | Yes | Yes | No | N/A | N/A | Yes | Yes |
| Nikbina et al., 2022 [37] | No | Yes | Yes | No | N/A | N/A | No | Yes |
| McKenzie et al., 2019 [32] | Yes | Yes | Yes | No | N/A | N/A | No | Yes |
| Rajput et al., 2022 [9] | Yes | Yes | Yes | No | N/A | N/A | No | Yes |
| Castiglia et al., 2009 [14] | No | Yes | Yes | Yes | N/A | N/A | No | Yes |
| Belengeanu et al., 2009 [13] | Yes | Yes | Yes | No | N/A | N/A | No | Yes |
| Mithwani et al., 2014 [34] | Yes | Yes | Yes | No | N/A | N/A | Yes | Yes |
| Migowa et al., 2010 [33] | Yes | Yes | Yes | Yes | N/A | N/A | No | Yes |
| Baldo et al., 2021 [61] | No | Yes | Yes | Yes | N/A | N/A | Yes | Yes |
| Shrestha et al., 2022 [47] | Yes | No | Yes | Yes | Partially | N/A | Yes | Yes |
| Dahlstrom et al., 1995 [17] | Yes | No | Yes | Yes | Partially | N/A | Yes | Yes |
| Choate et al., 1998 [15] | Yes | No | Yes | Yes | Partially | N/A | Yes | Yes |
| Hazukua et al., 2011 [24] | Yes | No | Yes | Yes | Partially | N/A | Yes | Yes |
| Shahada et al., 2022 [46] | Yes | No | Yes | Yes | Partially | N/A | Yes | Yes |
| Reyna-Villasmil et al., 2023 [44] | Yes | No | Yes | Yes | Partially | N/A | Yes | Yes |
| Lainingwala et al., 2023 [1] | Yes | No | Yes | Yes | Partially | N/A | Yes | Yes |
| Tahir et al., 2024 [51] | Yes | Yes | Yes | Yes | Partially | N/A | Yes | Yes |
| LIANG et al., 2019 [28] | Yes | Yes | Yes | Partially | No | N/A | Yes | Yes |
| Liu et al., 2021 [29] | Yes | Yes | Yes | Partially | No | N/A | Yes | Yes |
| Tran et al., 2023 [52] | Yes | Yes | Yes | Partially | No | N/A | Yes | Yes |
| Gunes et al., 2003[21] | Yes | Yes | Yes | No | No | Yes | Yes | Yes |
| Olney et al., 1993 [38] | Yes | Yes | Yes | No | No | Yes | Yes | Yes |
| Ukkal et al.i, 2015 [55] | Yes | Yes | Yes | Partially | No | Yes | Yes | Yes |
| Paria et al., 2015 [40] | Yes | Yes | Yes | Partially | No | Yes | Yes | Yes |
| Verma et al., 2019 [57] | Yes | Yes | Yes | Partially | No | Yes | Yes | Yes |
| Jilumudi et al., 2012 [26] | Yes | Yes | Yes | Partially | No | Yes | Yes | Yes |
| Salehin et al., 2013 [54] | Yes | Yes | Yes | Partially | No | Yes | Yes | Yes |
| Ugezu et al., 2017 [54] | Yes | No | No | No | No | N/A | Yes | Yes |
| Parikh et al., 2016 [41] | Yes | Yes | Yes | Yes | No | N/A | Yes | Yes |
| Liu, 2023 [30] | Yes | Yes | Yes | Yes | No | N/A | Yes | Yes |
| Montalvan-Suarez et al., 2019 [35] | Yes | Yes | Yes | Yes | No | N/A | Yes | Yes |

| Reference | Selection | Ascertainment | | Causality | | Reporting | | |
|---|---|---|---|---|---|---|---|---|
| | Leading Explanatory Questions | | | | | | | |
| | Q. 1 | Q. 2 | Q. 3 | Q. 4 | Q. 5 | Q. 6 | Q. 7 | Q. 8 |
| Moreau et al., 1999 [36] | Yes | No | No | Yes | No | N/A | Yes | No |
| Vijayakumari et al., 2020 [58] | Yes | No | No | No | No | N/A | Yes | No |
| Pet et al., 2016 [42] | Yes | Yes | Yes | No | No | N/A | Yes | Yes |
| Devnani et al., 2019 [18] | Yes | No | No | No | No | N/A | Yes | Yes |
| Zhou et al., 2021 [11] | Yes | Yes | Yes | No | No | N/A | Yes | Yes |
| Sanhal et al., 2013 [45] | Yes | Yes | Yes | Yes | No | N/A | Yes | Yes |
| Rajagopal et al., 2015 [43] | Yes | Yes | Yes | Yes | No | N/A | Yes | Yes |
| Fatima et al., 2014 [19] | Yes | No | No | No | No | N/A | Yes | No |
| Bahashwan et al., 2024 [8] | Yes | Yes | Yes | Yes | No | N/A | Yes | Yes |
| Vergotine et al., 2013 [56] | Yes | No | No | No | No | N/A | No | No |
| Arias-Perez et al., 2021 [60] | Yes | Yes | Yes | Yes | No | N/A | Yes | Yes |
| Suresh et al., 2004 [49] | Yes | No | No | No | No | N/A | Yes | No |
| Suzumori et al., 1991 [50] | Yes | Yes | Yes | No | No | N/A | Yes | Yes |
| Shruthi et al., 2017 [48] | Yes | Yes | Yes | No | No | N/A | Yes | Yes |
| Harvey et al., 2010 [23] | Yes | Yes | Yes | Yes | No | N/A | Yes | Yes |

**Table 4 Legend: Description of Methodological Quality Assessment Domains and Questions.**

The methodological quality of the included case reports and case series was evaluated using the **framework proposed by Murad, Sultan, Haffar, et al.** (**MMS**) [74]. This framework assesses four methodological domains: **Selection, Ascertainment, Causality, and Reporting**, comprising a total of eight structured questions (Q1–Q8).

**Selection:**

- **Q1:** Do the patient(s) represent the complete clinical experience of the investigator or center, or is the selection method insufficiently described such that other patients with similar presentations may not have been reported?

**Ascertainment:**

- **Q2:** Was the exposure adequately ascertained?
- **Q3:** Was the outcome adequately ascertained?

**Causality:**

- **Q4:** Were alternative explanations for the observed findings adequately ruled out?
- **Q5:** Was a challenge–rechallenge phenomenon documented?
- **Q6:** Was a dose–response relationship observed?
- **Q7:** Was the follow-up period sufficiently long for the outcome(s) to occur?

**Reporting:**

- **Q8:** Were the case(s) reported with sufficient detail to enable replication by other investigators or to allow clinicians to draw meaningful inferences applicable to their own practice?

generalizability of findings. However, limitations exist, including potential publication bias, heterogeneity in reporting clinical and genetic data, and the retrospective nature of included studies. The lack of long-term follow-up data also limits our ability to assess long-term outcomes in survivors. Future research should target the development of novel therapeutics and longitudinal outcome data.

## Conclusion

HI remains a life-threatening genetic disorder with significant morbidity and mortality. Early diagnosis, multidisciplinary management, and advances in genetic testing and targeted therapies hold promises for improving outcomes. However, challenges such as high infection rates, respiratory complications, and failure to thrive persist. Further research is needed to optimize management strategies and explore emerging therapeutic interventions that may enhance survival and quality of life in affected individuals.

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