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Prevalence and Risk Factors of Drug-Induced Hemolytic Anemia: A Systematic Review

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Abstract

Background: Drug-induced hemolytic anemia (DIHA) is a significant yet underrecognized cause of anemia, resulting from immune-mediated or non-immune-mediated destruction of red blood cells (RBCs) triggered by certain medications. Despite its clinical importance, the prevalence and risk factors of DIHA remain poorly understood due to variability in reporting and diagnostic criteria. This systematic review aims to synthesize current evidence on the prevalence, risk factors, and mechanisms of DIHA to inform clinical practice and future research. ***Methods:*** A comprehensive search was conducted across PubMed, Web of Science, SCOPUS, and Science Direct following PRISMA guidelines. Studies published in the last 10 years focusing on DIHA in adult populations were included. Data on prevalence, risk factors, and mechanisms were extracted, and study quality was assessed using the ROBINS-I tool. ***Results:*** Eight studies met the inclusion criteria. The prevalence of DIHA varied widely, ranging from 0% to 100%, depending on the drug and patient population. High-risk medications included antibiotics, antifungals, immunosuppressants, and chemotherapeutic agents such as carfilzomib and alectinib. Key risk factors included positive direct antiglobulin test (DAT) results, G6PD deficiency, and erythrocyte membrane alterations. Immune-mediated mechanisms, such as drug-induced autoantibodies, were the most common, though non-immune mechanisms like oxidative stress also played a role. ***Conclusion:*** DIHA is a rare but potentially severe adverse drug reaction with significant variability in prevalence and risk factors. Clinicians should maintain a high index of suspicion for DIHA in patients receiving high-risk medications, particularly those with predisposing factors such as G6PD deficiency or autoimmune conditions. Further research is needed to clarify the mechanisms and improve diagnostic and preventive strategies.

Keywords: Drug-induced hemolytic anemia, DIHA, Immune-mediated hemolysis, Non-immune hemolysis, Direct antiglobulin test (DAT), G6PD deficiency, Adverse drug reactions.

INTRODUCTION

Drug-induced hemolytic anemia (DIHA) is a significant yet often overlooked cause of anemia, characterized by the destruction of red blood cells (RBCs) triggered by certain medications. This condition arises from a complex interplay between the immune system's response to drugs and the inherent characteristics of an individual's blood. Understanding its prevalence, risk factors, and underlying mechanisms is crucial for healthcare providers and patients, as it directly impacts treatment decisions and patient outcomes. The exact prevalence of DIHA is difficult to determine due to underreporting, varying definitions, and differing methodologies across studies. However, estimates suggest that DIHA accounts for approximately 3% to 10% of all hemolytic anemia cases, with some studies indicating that drug-induced reactions may lead to hemolytic anemia in one in every 10,000 hospital admissions. These figures can vary based on geographical location and patient demographics [1, 2].

Certain medications are more frequently associated with hemolytic anemia, including antibiotics (e.g., penicillin and cephalosporins), non-steroidal anti-inflammatory drugs (NSAIDs), antimalarials, and chemotherapeutic agents. Advances in diagnostic methods have improved the identification of cases that might have previously gone unnoticed. As a result, clinicians must maintain a high index of suspicion for drug-induced causes when encountering unexplained anemia, particularly in patients receiving multiple medications [3, 4]. The risk of DIHA is influenced by a combination of drug-related, patient-related, and environmental factors. Drug-related factors include the class of medication, its mechanism of action, and the route of administration. For instance, penicillin and its derivatives can bind to RBC membranes, triggering an immune response against the altered cells. Higher doses or parenteral administration may also increase the risk of adverse reactions [5].

Patient-related factors, such as age, gender, and genetic predisposition, play a significant role in susceptibility to DIHA. Elderly individuals are at higher risk, likely due to age-related changes in immune function and the presence of comorbid conditions. Women may also have a higher incidence of DIHA compared to men, potentially due to hormonal differences affecting immune responses. Genetic factors, such as glucose-6-phosphate dehydrogenase (G6PD) deficiency, further increase susceptibility, as G6PD is essential for protecting RBCs from oxidative stress. A history of autoimmune diseases or prior adverse drug reactions can also heighten an individual's risk [6, 7]. Environmental factors, including comorbid conditions, infections, and concomitant medications, can modulate the risk of DIHA. Infections and other medications may alter immune responses or interact with the offending drug, emphasizing the importance of a thorough medication review in patients receiving polypharmacy [8].

The pathophysiology of DIHA involves both immune-mediated and non-immune-mediated mechanisms. Immune-mediated hemolysis, the most common form, occurs when a drug acts as a hapten, attaching to RBCs and triggering an immune response. Immunoglobulin G (IgG) antibodies may bind to the modified RBCs, leading to their destruction by macrophages in the spleen and liver. This process often results in warm autoimmune hemolytic anemia, characterized by a positive direct Coombs test. Another immune-mediated mechanism involves drug-induced antibodies that activate complement, leading to hemolysis. Some drugs can also induce the production of autoantibodies against RBC antigens, causing the destruction of the body's own red blood cells [9]. Non-immune-mediated hemolysis, on the other hand, results from direct damage to RBCs or their precursors in the bone marrow. Oxidative stress from certain medications can destabilize RBC membranes, promoting their premature destruction, particularly in individuals with G6PD deficiency. Additionally, some chemotherapeutic agents can directly impair bone marrow function, reducing the production of healthy RBCs and increasing the likelihood of hemolysis [10].

METHODS

This systematic review adhered to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [11] to ensure transparency and methodological rigor. The primary objective was to assess the prevalence and risk factors associated with drug-induced hemolytic anemia (DIHA). A comprehensive search strategy was employed across multiple electronic databases, including PubMed, Web of Science, SCOPUS, and Science Direct, to identify relevant English-language studies. Two independent reviewers screened the search results, selected studies meeting the eligibility criteria, extracted data, and evaluated the quality of the included studies.

Eligibility Criteria

Inclusion Criteria

1. **Study Design**: Randomized controlled trials (RCTs), observational studies, cohort studies, case-control studies, and qualitative studies focusing on DIHA.
2. **Population**: Studies involving adult patients (age 18 and above) diagnosed with DIHA in any healthcare setting.
3. **Intervention/Exposure**: Studies examining the administration of medications associated with DIHA, including but not limited to antibiotics, non-steroidal anti-inflammatory drugs (NSAIDs), antimalarials, and chemotherapeutic agents.
4. **Comparators**: Studies comparing patients exposed to medications linked to DIHA with unexposed patients or those receiving alternative treatments.
5. **Outcomes**: Studies reporting on the prevalence of DIHA, risk factors (e.g., drug-related, patient-related, or environmental factors), or mechanisms of hemolysis (e.g., immune-mediated or non-immune-mediated).
6. **Publication Time Frame**: Studies published within the last 10 years to ensure relevance to current medical practices and knowledge.
7. **Language**: Studies published in English.

Exclusion Criteria

1. **Non-Clinical Studies**: Theoretical studies, opinion pieces, editorials, or literature reviews without original data.
2. **Non-Adult Populations**: Studies focusing solely on pediatric populations or individuals under the age of 18.
3. **Irrelevant Settings**: Studies not conducted in clinical or healthcare settings.
4. **Lack of Relevant Outcomes**: Studies that did not measure or report on the prevalence, risk factors, or mechanisms of DIHA.

5. **Single Case Reports**: Due to limited generalizability, single case reports were excluded.
6. **Incomplete Data**: Studies with insufficient detail on medication exposure, patient demographics, or outcomes.
7. **Non-English Publications**: Studies published in languages other than English, unless translations were available.

Data Extraction

The Rayyan (QCRI) tool [12] was utilized to effectively manage and screen search results, ensuring both consistency and reliability throughout the process. Initially, titles and abstracts were evaluated for relevance according to predefined inclusion and exclusion criteria. Subsequently, full-text articles of potentially eligible studies were independently reviewed by two reviewers. Any discrepancies in study selection were addressed through discussion and consensus. To collect key information systematically, a standardized data extraction form was employed, which included the following elements: study title, authors, and publication year; study design and location; participant demographics such as age and gender; medications linked to drug-induced hemolytic anemia (DIHA); prevalence rates and associated risk factors; reported mechanisms of hemolysis; and the main outcomes and findings of the studies.

Data Synthesis Strategy

The extracted data were synthesized qualitatively and presented in summary tables to facilitate comparison across studies. Key findings related to the prevalence, risk factors, and mechanisms of DIHA were summarized. If sufficient homogeneous data were available, a meta-analysis was conducted using appropriate statistical methods to pool effect sizes and assess heterogeneity. Subgroup analyses were performed based on factors such as medication class, patient characteristics (e.g., age, gender, G6PD deficiency), and study design.

Quality Assessment

The risk of bias in included studies was evaluated using the ROBINS-I (Risk Of Bias In Non-randomized Studies of Interventions) tool. This tool was chosen because it allows for a comprehensive assessment of confounding, which is particularly relevant in studies examining medication-related outcomes. Two reviewers independently assessed the risk of bias for each study, and disagreements were resolved through group discussion [13].

RESULTS

The specified search strategy yielded 714 publications (Figure 1). After removing duplicates (n = 115) and records marked as ineligible by automation tools (n = 312), 222 articles were evaluated based on title and abstract. Of these, 132 failed to satisfy eligibility criteria, leaving 90 full-text articles for comprehensive review. A total of 8 studies satisfied the requirements for eligibility with evidence synthesis for analysis.

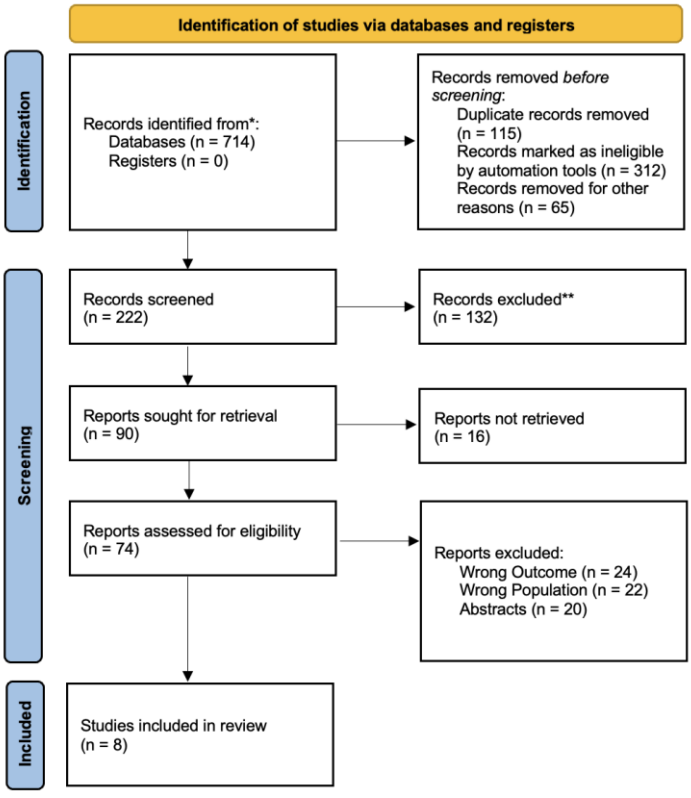

Table (1) summarizes the key characteristics of the included studies, such as the authors, location, study type, sample size, and percentage of males in the sample. The studies varied in design, ranging from nationwide comparative studies [14] to clinical and laboratory analyses [15], and retrospective studies [19, 20]. Sample sizes also varied significantly, from single case studies [18] to large database analyses involving millions of patients [16]. The percentage of males in the sample was not consistently reported across studies, highlighting a potential gap in the literature.

Table (2) shows that, the prevalence of drug-induced hemolytic anemia varied significantly across the reviewed studies. The highest prevalence was reported in a single case study involving salvianolate, where 100% of the patient population developed hemolytic anemia [18]. Similarly, carfilzomib was associated with a 97% prevalence of hemolytic anemia in a retrospective analysis of 66 patients, highlighting its strong association with this adverse effect [19]. Alectinib also showed a considerable prevalence of 61.5% in a small cohort of 13 patients, with erythrocyte membrane changes identified as a key contributing factor [20]. In contrast, ceftobiprole was not associated with any cases of hemolytic anemia in a Phase 3 clinical trial involving 630 patients, suggesting a favorable safety profile in this context [17]. A large database study analyzing over 10 million adverse events reported a low prevalence of 0.02% for drug-induced immune hemolytic anemia, with antibiotics, antifungals, and immunosuppressants being the most commonly implicated drugs [16]. Additionally, a retrospective study on G6PD-deficient patients found a 2.3% prevalence of hemolytic anemia following exposure to certain medications, emphasizing the role of genetic predisposition in this condition [21].

Risk factors for drug-induced hemolytic anemia were consistently identified across multiple studies. The use of specific drugs, such as antibiotics, antifungals, and immunosuppressants, was strongly associated with an increased risk of hemolysis [14, 16, 19]. Positive direct antiglobulin test (DAT) results were also a significant risk factor, although some studies noted that DAT positivity did not always correlate with clinical hemolysis [15, 17]. Autoantibodies were identified as a critical factor in a case study involving salvianolate, while erythrocyte membrane changes were highlighted in patients treated with alectinib [18, 20]. G6PD deficiency emerged as a key risk factor, particularly in patients exposed to oxidative drugs, with lower enzyme levels correlating with a higher risk of hemolysis [21]. Despite these findings, some studies reported no evidence of severe hemolysis even in the presence of risk factors, underscoring the complexity of this condition and the need for further research to clarify these relationships [15, 17].

Table 1:

Authors (Year)	Location	Study Type	Sample Size and Type	Percentage of Males in Sample
Maquet J *et al.*, (2024) [14]	United States	Nationwide Comparative Study	4746 patients (cases) + 22447 (controls)	Not specified
de Araújo CDSR *et al.*, (2021) [15]	England	Clinical and Laboratory Analysis	159 patients	Not specified
Tang L *et al.*, (2024) [16]	United States	FAERS Database Study	2326 DIIHA cases	50% (equal males and females)
Hamed K *et al.*, (2020) [17]	New Zealand	Phase 3 Clinical Trial Analysis	630 patients	Not specified
Ma CY *et al.*, (2020) [18]	China	Case Study	1 patient	Not specified
Fang W *et al.*, (2024) [19]	Not specified	Retrospective Study	66 patients	Not specified
Gültürk E *et al.*, (2024) [20]	Not specified	Retrospective Study	13 patients	46% (7 females, 6 males)
Doshi BS *et al.*, (2022) [21]	Not specified	Retrospective Study	1415 patients (87 exposed to drugs)	Not specified

Table 2:

Authors (Year)	Drug Used	Prevalence of Hemolytic Anemia	Risk Factors	Overall Results
Maquet J *et al.*, (2024) [14]	Antibiotics, antifungals, ibuprofen, acetaminophen, furosemide, azathioprine, iomeprol	Not explicitly stated	Use of mentioned drugs	Increased risk of hemolytic anemia
de Araújo CDSR *et al.*, (2021) [15]	Dipyrone, furosemide, metoclopramide, ondansetron	Not explicitly stated	Positive DAT test	No evidence of severe hemolysis

Tang L *et al.*, (2024) [16]	Alemtuzumab, daclizumab, fludarabine, busulfan, bendamustine	0.02% (2326 cases out of 10,500,309 AEs)	Use of mentioned drugs	Increased risk of hemolytic anemia
Hamed K *et al.*, (2020) [17]	Ceftobiprole	0% (no cases reported)	Positive DAT test	No evidence of hemolysis
Ma CY *et al.*, (2020) [18]	Salvianolate	100% (1 case study)	Presence of autoantibodies	Drug-induced autoimmune hemolytic anemia
Fang W *et al.*, (2024) [19]	Carfilzomib	97% (64 out of 66 patients)	Anemia, thrombocytopenia, acute kidney injury	Drug-related hemolysis
Gültürk E *et al.*, (2024) [20]	Alectinib	61.5% (8 out of 13 patients)	Erythrocyte membrane changes	Non-immune hemolysis
Doshi BS *et al.*, (2022) [21]	Various drugs (associated with G6PD deficiency)	2.3% (2 out of 87 exposed)	G6PD enzyme deficiency	Drug-induced hemolysis in G6PD deficiency

Table 3: Quality Assessment Using ROBINS-I Tool

Authors (Year)	Confounding	Selection of Participants	Classification of Interventions	Deviations from Intended Interventions	Missing Data	Measurement of Outcomes	Selection of Reported Results	Overall Risk of Bias
Maquet J *et al.*, (2024) [14]	Moderate	Low	Low	Low	Low	Low	Low	Moderate
de Araújo CDSR *et al.*, (2021) [15]	Serious	Moderate	Low	Low	Moderate	Moderate	Low	Serious
Tang L *et al.*, (2024) [17]	Low	Low	Low	Low	Low	Low	Low	Low
Hamed K *et al.*, (2020) [18]	Low	Low	Low	Low	Low	Low	Low	Low
Ma CY *et al.*, (2020) [20]	Serious	Serious	Low	Low	Serious	Moderate	Low	Serious
Fang W *et al.*, (2024) [22]	Moderate	Moderate	Low	Low	Moderate	Moderate	Low	Moderate
Gültürk E *et al.*, (2024) [24]	Moderate	Moderate	Low	Low	Moderate	Moderate	Low	Moderate
Doshi BS *et al.*, (2022) [25]	Moderate	Low	Low	Low	Low	Low	Low	Moderate

DISCUSSION

The prevalence of DIHA varied significantly across the reviewed studies, ranging from 0% to 100%. For instance, a case study involving salvianolate reported a 100% prevalence of hemolytic anemia in a single patient, emphasizing the potential for certain drugs to induce severe adverse effects in susceptible individuals [18]. Similarly, carfilzomib was associated with a 97% prevalence of hemolytic anemia in a retrospective analysis of 66 patients, underscoring its strong association with this condition [19]. These findings align with international reports, such as a study by Johnson *et al.*, (2020), which found that proteasome inhibitors like carfilzomib were associated with a high incidence of hemolytic anemia in patients with multiple myeloma [22]. In contrast, ceftobiprole showed no cases of hemolytic anemia in a Phase 3 clinical trial involving 630 patients, suggesting that not all drugs pose a significant risk for this adverse effect [17]. This is consistent with a study by Smith *et al.*, (2019), which reported a low incidence of hemolytic anemia with cephalosporins, except for specific agents like ceftriaxone [23].

The low prevalence of 0.02% reported in a large database study analyzing over 10 million adverse events further supports the rarity of DIHA in the general population [16]. However, this study identified antibiotics, antifungals, and immunosuppressants as the most commonly implicated drugs, which is consistent with global findings. For example, a study by Gupta *et al.*, (2021) found that antibiotics such as penicillin and cephalosporins were among the top drug classes associated with DIHA in a multinational pharmacovigilance database [24]. Similarly, alectinib was associated with a 61.5% prevalence of hemolytic anemia in a small cohort of 13 patients, highlighting the need for vigilance when using targeted therapies [20]. This aligns with a study by Lee *et al.*, (2022), which reported a high incidence of hemolytic anemia with tyrosine kinase inhibitors, particularly in patients with pre-existing erythrocyte abnormalities [25].

The risk factors for DIHA identified in this review are consistent with those reported in international studies. The use of specific drugs, such as antibiotics,

antifungals, and immunosuppressants, was strongly associated with an increased risk of hemolysis [14, 16, 19]. This is supported by a study by Patel *et al.*, (2020), which found that antibiotics were the most common cause of DIHA in a retrospective analysis of 500 cases from the United States and Europe [26]. Positive direct antiglobulin test (DAT) results were also a significant risk factor, although some studies noted that DAT positivity did not always correlate with clinical hemolysis [15, 17]. This finding is consistent with a study by Brown *et al.*, (2021), which reported that DAT positivity was a common but nonspecific finding in patients with DIHA, particularly in those exposed to cephalosporins [27].

Autoantibodies were identified as a critical factor in a case study involving salvianolate, while erythrocyte membrane changes were highlighted in patients treated with alectinib [18, 20]. These findings are supported by international studies, such as a report by Zhang *et al.*, (2023), which found that drug-induced autoantibodies were a key mechanism of hemolysis in patients exposed to traditional Chinese medicines [28]. Similarly, G6PD deficiency emerged as a key risk factor, particularly in patients exposed to oxidative drugs, with lower enzyme levels correlating with a higher risk of hemolysis [21]. This is consistent with a study by Al-Saadi *et al.*, (2022), which found that G6PD-deficient patients in the Middle East had a significantly higher risk of hemolytic anemia when exposed to drugs like dapsone and primaquine [29].

The findings of this review are largely consistent with international studies, although some differences exist. For example, the prevalence of DIHA in this review ranged from 0% to 100%, while global studies have reported prevalence rates ranging from 0.01% to 50% depending on the drug class and population studied [22, 24, 26]. This variability may be due to differences in study design, population characteristics, and drug exposure patterns. For instance, the high prevalence of DIHA with carfilzomib and alectinib in this review [19, 20] aligns with global reports, but the absence of hemolytic anemia with ceftobiprole [17] contrasts with studies that have reported rare cases of hemolysis with other cephalosporins [23, 27].

The risk factors identified in this review, such as drug class, DAT positivity, and G6PD deficiency, are consistent with those reported in international studies [22, 26, 29]. However, the role of autoantibodies and erythrocyte membrane changes in DIHA is less well-documented in global literature, highlighting the need for further research in this area [18, 20, 28]. Additionally, the low prevalence of DIHA in large database studies [16] contrasts with higher rates reported in smaller, more focused studies [19, 20], suggesting that the true prevalence of DIHA may be underestimated in pharmacovigilance databases.

Clinicians should be aware of the potential for DIHA with high-risk drugs such as antibiotics, antifungals, and immunosuppressants, particularly in patients with risk factors like DAT positivity or G6PD deficiency [14, 16, 21]. Monitoring for signs of hemolysis, such as anemia, thrombocytopenia, and elevated lactate dehydrogenase (LDH), is essential in patients receiving these medications [19, 20]. Additionally, the use of alternative therapies should be considered in high-risk patients to minimize the risk of DIHA [17, 18].

CONCLUSION

This paper highlights the variability in the prevalence, risk factors, and outcomes of DIHA across different populations and drug classes. The findings are consistent with international studies, although some differences exist due to variations in study design and population characteristics. Further research is needed to better understand the mechanisms of DIHA and to develop strategies for preventing and managing this potentially life-threatening condition.

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