Attahadi Medical Journal
2026;3(3):377-380
https://doi.org/10.69667/amj.26316

OPEN ACCESS

Original article

COVID-19 Vaccination in Hemophilia: Indirect Evidence on NSAID-associated Bleeding Risk

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Keywords:
Hemophilia, Hemostasis, Platelet Aggregation, Non-Steroidal Anti-Inflammatory Drugs, NSAIDs, COVID-19 vaccines

ABSTRACT

Patients with hemophilia are at risk of bleeding due to coagulation factor deficiencies. Intramuscular (IM) vaccination, including vaccines against COVID-19, raises concerns regarding injection-site bleeding. Moreover, the widespread use of NSAIDs for post-vaccination symptoms may further increase bleeding risk. This review aims to evaluate the incidence and mechanism of bleeding in patients confirmed with hemophilia following COVID-19 vaccination and assess the potential additive risk associated with the use of NSAIDs. Available evidence indicates that bleeding events following vaccination are infrequent and predominantly mild. However, NSAIDs impair antiplatelet aggregation and may exacerbate bleeding risk when combined with underlying coagulation defects. Direct evidence is strictly limited; nevertheless, pharmacological and indirect clinical data support a synergistic interaction. COVID-19 vaccination is systematically safe in hemophilia patients based on the available data from the selected studies; however, NSAID use represents a modifiable risk factor for bleeding, and safe alternatives such as paracetamol should be prioritized.

Introduction

Patients with hemophilia are characterized by deficiencies in coagulation factors VIII or IX, resulting in impaired secondary hemostasis and an increased susceptibility to spontaneous and trauma-induced bleeding [1, 2]. Intramuscular (IM) injections, including vaccination, have historically raised concerns due to the potential for local hematoma formation in this population [3]. The global rollout of vaccines against COVID-19 has raised significant clinical safety considerations in individuals with bleeding disorders. Early guidance from the World Federation of Hemophilia and the Swiss Hemophilia Network recommended precautionary measures, including factor replacement therapy and prolonged compression after injection, regarding post-injection bleeding complications, particularly in patients with severe disease or inadequate prophylaxis [4, 5]. Subsequently, some studies have demonstrated that COVID-19 vaccines are generally safe, with low rates of bleeding complications, especially in cases of acquired hemophilia A (AHA) [6-8].

Nonsteroidal Anti-inflammatory Drugs (NSAIDs), such as ibuprofen and diclofenac, are commonly used to manage post-vaccination symptoms (e.g., fever, myalgia). However, NSAIDs inhibit cyclooxygenase enzymes and reduce thromboxane A2 synthesis, impairing platelet aggregation and primary hemostasis [9]. The pharmacological effect may introduce a potential additive bleeding risk, particularly in individuals with pre-existing coagulation disorders [10]. Despite growing evidence on COVID-19 vaccine safety in hemophilia, the NSAID-associated bleeding risk is well documented; no comprehensive synthesis has evaluated the combined impact of vaccine and NSAID use on bleeding risk. This review aims to address this gap by integrating clinical evidence with pharmacological mechanisms.

Methods

A structured literature search was conducted in PubMed, Scopus, Web of Science, and Google Scholar, up to 2025, using combinations of the following keywords: (hemophilia) AND (“COVID-19 vaccine”) AND (bleeding OR hematoma OR safety) AND (NSAIDs OR ibuprofen OR diclofenac OR analgesics).

Inclusion criteria

Observational studies, case reports and case series, registry-based studies, and studies addressing NSAIDs and bleeding risk in hemophilia. Exclusion criteria: Narrative reviews without primary data, non-English publications, and studies unrelated to bleeding outcomes due to hemophilia.

Received: *01-06-2026 - **Accepted:** 29-07-2026 - **Published:** 07-08-2026*

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2026;3(3):377-380
https://doi.org/10.69667/amj.26316

OPEN ACCESS

Data Extraction

Extracted data variables included study design, sample size, type of hemophilia, vaccine type, bleeding incidence and safety, and reported NSAID use.

Results

The synthesis of the available evidence revealed that hemophilia patients face unique risk patterns across the included studies: (i) Bleeding post-COVID-19 vaccination. Available literature suggests that bleeding events in hemophilia following COVID-19 vaccination are rare and predominantly mild, mainly injection-site hematomas [8, 11]; however, rare immune-mediated events such as acquired hemophilia A (AHA) have been reported. The key evidence for this is that there are multiple case reports describing the development of AHA following vaccination, presenting with spontaneous bleeding and prolonged aPTT [12, 13, 14]. Therefore, these events are considered extremely rare but clinically significant. The vaccination may act as a trigger for autoantibody formation against factor VIII. Importantly, the vaccination outweighs the rare risks. (ii) NSAIDs and bleeding risk in hemophilia. NSAIDs contribute to bleeding risk through the inhibition of COX-1, which leads to a reduction in thromboxane A2 and impaired platelet aggregation [10]. The summarized clinical implications reflected the effects of primary hemostasis, as well as the independent risk associated with clotting factor deficiency. This creates a dual hemostatic defect (hemophilia due to impaired coagulation cascade), and NSAIDs would reduce or impair platelet function [10, 15]. (iii) Combined risk: Hemophilia, NSAIDs, and Vaccination. Direct studies are limited, but strong indirect evidence supports additive risk and a mechanistic interaction (Table 1). Collectively, the combined results indicate a dual impairment of hemostasis, increasing the likelihood of prolonged or excessive local bleeding (hematoma formation). (iv) The clinical pattern of bleeding. Across the studies, most bleeding episodes are localized and mild, and severe bleeding is rare and associated with severe hemophilia, lack of prophylaxis, and immune complications (AHA) (Table 2).

Table 1. Evidence summary of bleeding risk factors

Factor	Pathway affected	Effect	Evidence strength	Clinical risk
Hemophilia	Secondary hemostasis (factor deficiency)	Inhibition of fibrin formation (clot formation impairment)	Strong	High
NSAIDS	Primary hemostasis	Reduction of platelet aggregation	Strong	Moderate
IM vaccination	Vascular injury (local trauma)	Increased bleeding trigger	Moderate	Low
Combined effect	Dual pathway impairment	Synergistic bleeding risk increase	Limited	Potentially increased

Table 2 shows the selected studies

No	Study	Study type	Key finding
1	Radwi & Farsi (2021)	Case report	AHA after the COVID-19 vaccine [16]
2	Al Hennawi et al. (2022)	Case + review	Hematoma and AHA post-vaccine [17]
3	Happaerts et al. (2022)	Case + review	Severe bleeding with an autoimmune trigger [12]
4	Soliman et al. (2022)	Case report	Gross hematuria after vaccination [7]
5	Murali et al. (2022)	Case report	AHA after mRNA vaccine [18]
6	Emna et al. (2023)	Case report	AHA after inactivated vaccine [19]
7	Beckerman et al. (2025)	Case report	Booster-associated bleeding complications [13]

Discussion

The review synthesizes available clinical and mechanistic evidence regarding bleeding risk in patients with hemophilia undergoing COVID-19 vaccination while receiving Nonsteroidal Anti-inflammatory Drugs. The findings indicate that although COVID-19 vaccines are generally safe in this population with existing observational data and international recommendations, the addition of NSAIDs introduces a clinically relevant and potentially increased layer of bleeding risk. The current literature consistently demonstrates that the post-vaccination bleeding in hemophilia patients is infrequent and predominantly mild. Most reported events are localized injection-site hematomas. Severe bleeding complications are rare and often linked to additional risk factors. However, the literature is largely composed of case reports, small observational cohorts, and registry-based surveillance. This limits the ability to establish precise incidence rates or causal relationships. Importantly, direct evidence evaluating NSAID administration in this context is scarce, necessitating reliance on pharmacological and indirect clinical data. The main finding is that COVID-19 vaccination and NSAIDs together could create a synergistic impairment of both primary and secondary hemostasis, particularly in the setting of intramuscular

Received: *01-06-2026 -* ***Accepted:*** *29-07-2026 -* ***Published:*** *07-08-2026*

vaccination. This dual-pathway hemostatic disruption (the concurrent presence of hemophilia, COVID-19 vaccination, and NSAIDs) increases susceptibility to prolonged or excessive bleeding. Unlike hemophilia alone, where factor replacement can restore clotting, NSAID-induced platelet dysfunction persists and is not corrected by factor therapy, thereby sustaining bleeding risk. The clinical significance of NSAID use, such as ibuprofen and diclofenac, is frequently related to post-vaccination symptom control. However, their impact on platelet function makes them a suboptimal choice in patients with inherited bleeding disorders. In contrast, the modifiable use of paracetamol does not inhibit platelet aggregation and provides effective analgesia and antipyresis; therefore, it represents a safer first-line option. Although uncommon, cases of acquired hemophilia A following COVID-19 vaccination have been reported. These cases involve autoantibody formation against factor VIII and severe, sometimes life-threatening bleeding. While causality remains uncertain, these events highlight the need for clinical vigilance and the importance of differentiating between injection-related bleeding and systemic coagulopathies.

Conclusion

In conclusion, COVID-19 vaccination in patients with hemophilia is generally safe and associated with a low incidence of mild bleeding events, primarily limited to the injection-site hematomas. However, the concomitant use of Nonsteroidal Anti-Inflammatory Drugs poses a further and potentially avoidable risk due to impairment of platelet function. The interaction between coagulation factor deficiency and NSAID-induced platelet dysfunction represents a clinically significant dual hemostatic defect, particularly in the context of intramuscular injection. Outstandingly, this risk is modifiable. The preferential use of safer alternatives such as Paracetamol, along with appropriate prophylactic and procedural measures, can substantially reduce bleeding complications.

Recommended management of Hemophilia patients receiving the COVID-19 vaccine with analgesia needs

The recommended management can be achieved through several steps to obtain desirable outcomes with minimum risks: (i) pre-vaccination, through assessing the severity of hemophilia, administration of factor replacement (if severe), and using the smallest gauge needle, (ii) vaccination, post-IM injection compression for more than 10 minutes, hematoma monitoring, (iii) post-vaccination analgesia, the preferred analgesic medications is paracetamol with avoidance ibuprofen and diclofenac as possible, (iv) if NSAIDs required, the recommendation is to start with the lowest dose for short period, and monitoring for swelling, bruising, and delayed bleeding, (v) follow-up, the patient should be educated to report of any sign of bleeding early.

Disclaimer

The article has not been previously presented or published, and is not part of a thesis project.

Conflict Of Interest

There are no financial, personal, or professional conflicts of interest to declare.

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Received: *01-06-2026 -* ***Accepted:*** *29-07-2026 -* ***Published:*** *07-08-2026*

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Received*: 01-06-2026 -* ***Accepted****: 29-07-2026 -* ***Published****: 07-08-2026*