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Original Article

# Unveiling the Safety Profile of Rituximab in Pemphigus Vulgaris: A Cross-Sectional Insight into Adverse Reactions

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**Abstract**

**Introduction:** Pemphigus vulgaris (PV) is one of the most prevalent autoimmune skin-blistering diseases, characteristically emerging between the ages of 40 and 60, caused by antibodies targeting the desmoglein protein in the skin. Rituximab, an anti-CD20 monoclonal antibody, received FDA approval in 2018 for PV treatment, particularly for the patients unresponsive to the conventional therapies. Due to the efficacy, rituximab has been accepted as an effective therapeutic choice for PV.

**Methods:** This cross-sectional retrospective study analyzed data from medical documentations of pemphigus vulgaris patients who have been treated at Sina Hospital from April 2018 to March 2022. The study was designed to evaluate the incidence of rituximab's common adverse effects and explore any correlations with patients' demographics.

**Results:** Among the patients reviewed, 36.3% received rituximab during at least one hospitalization, with 8.45% experiencing at least one adverse drug reaction, including one life-threatening event. The most prevalent adverse effect was injection-related hypersensitivity reactions, primarily manifesting as pruritus. Other complications, such as opportunistic infections, hepatic dysfunction and leukopenia followed in frequency. There were no reported fatalities attributed to the treatment in the study population.

**Conclusion:** The predominance of injection-related hypersensitivity reactions among adverse drug reactions aligns with findings from other studies. However, the lower incidence rate at this center suggests that pre-treatment protocols may lessen such reactions. The observed long-term complications were predominantly infections, notably herpes virus reactivations, reflecting the immunosuppressive effect of rituximab, consistent with global reports from similar research.

## Introduction

Pemphigus vulgaris (PV) is the most prevalent autoimmune blistering dermatologic disease, characterized by antibody production against a skin protein called desmoglein.[1,2] Typically manifesting between 40 to 60 years of age, PV is categorized into two primary subtypes: pemphigus vulgaris, accounting for 70-90% of cases, and pemphigus foliaceus.[3] The incidence rate of pemphigus vulgaris is found to be approximately 2.83 per million person-years.[4] Severe cases Significantly impact the quality of life, imposing an annual patient cost of approximately 3,995 euros.[5]

Historically, prior to the 1950s, PV had a mortality rate of about 75%,[6] which is largely reduced to below 10% following the use of corticosteroids.[7] Oral corticosteroids, guided by clinical severity and patient response, forms the basis of a standard treatment regimen, often accompanied by adjunctive therapies in more severe cases to optimize patient outcomes and minimize adverse effects. Rituximab, an anti-CD20 monoclonal antibody, introduced in 1997 for various autoimmune and hematological cancers, received FDA approval in June 2018 for moderate to severe PV.[8] Rituximab targets CD20 on B lymphocytes, leading to their depletion without affecting antibody-producing plasma cells.[9] The drug is usually well-tolerated and its effects last for about six months, but its use has been linked to hypersensitivity reactions including type 1 (IgE-dependent or independent), type 3, 4, or a combination of these.[10] The typical symptoms of type 1 hypersensitivity reactions following the immediate release of histamine granules commonly include flushing, urticaria (hives), itching, shortness of breath, and wheezing, with rare cases leading to life-threatening hypotension or anaphylactic shock.[11] Consensus within the medical professionals suggests that in instances where patients exhibit severe hypersensitivity reactions, subsequent administrations of the drug should be avoided. Conversely, for mild to moderate reactions, the approach of desensitization is

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**Study Highlights**

***What is current knowledge?***

- Pemphigus vulgaris (PV) is an autoimmune skin-blistering disease characterized by auto-antibodies targeting desmoglein proteins. Rituximab, an anti-CD20 monoclonal antibody, has been recognized as a standard treatment protocol for moderate to severe cases since its FDA approval in 2018, reducing mortality compared to historical corticosteroid-only regimens. While the drug is generally well-tolerated, current clinical knowledge identifies injection-related hypersensitivity reactions (HSRs) as the most frequent acute adverse events. Additionally, its immunosuppressive effects carry known risks for long-term complications, including opportunistic infections and the reactivation of latent viruses.

***What is new here?***

- This study demonstrates a notably lower incidence of hypersensitivity reactions (19.17%) compared to the 77–90% rates reported in many global clinical trials. These findings suggest that the specific pre-treatment protocol utilized—consisting of intravenous chlorpheniramine, hydrocortisone, and oral acetaminophen—may be more effective at reducing acute reactions than standard protocols elsewhere. Furthermore, the research provides rare evidence of organ-specific toxicity, documenting a confirmed case of drug-induced cholestasis. The data also reveals a gender-based disparity, showing that female patients in this study experienced adverse effects more frequently than males, underscoring the potential need for more vigilant, gender-specific monitoring in clinical practice.

considered an appropriate strategy.[12] In certain medical settings, the administration of corticosteroids such as methylprednisolone, along with anti-histamines and acetaminophen, aims to decrease the probability of type 1 hypersensitivity reactions.[13] This combination therapy is employed to mitigate the immune system's overreaction to allergens or other triggers, thereby reducing the risk of severe allergic responses.

In addition to its known hypersensitivity reactions, Rituximab has other side effects, including opportunistic infections like hepatitis B reactivation in those with previous infection, and latent infections such as tuberculosis and hepatitis C.[14,15,16] Cytopenia, particularly neutropenia and thrombocytopenia, are common, especially in patients with malignancies.[17] Less common adverse effects include pulmonary edema, cardiovascular complications (including ischemic heart disease and arrhythmias), and increased susceptibility to infections like herpes simplex and pneumocystis pneumonia.[18,19,20,21]

The aim of this study is to evaluate the prevalence of Rituximab's common drug-related side effects in Pemphigus vulgaris patients. We focused on assessing the frequency and nature of adverse reactions, particularly hypersensitivity responses, and exploring any age and gender correlations among PV patients who received the treatment. The study also aims to enhance understanding of Rituximab's safety profile in PV treatment and examine the effectiveness of pre-treatment protocols.

## Material and Methods

This cross-sectional study was conducted over a four-year period from the beginning of April 2018 to the end of March 2022 at the Sina hospital, Tabriz. We employed a census method for sampling. The study sources comprised hospital inpatient records, outpatient clinic files, and telephone interviews about long-term complications following outpatient visits to the dermatology clinic. For complications necessitating imaging or additional tests, reliance was placed on previously conducted procedures. The study meticulously recorded acute and long-term adverse effects post-Rituximab treatment. Acute effects ranged from itching and rashes to anaphylactic shock, necessitating immediate medical attention. Long-term risks involved reactivation of latent infections like herpes, opportunistic infections, cytopenia characterized by specific blood cell count thresholds, hepatic complications, and reactivation of the JC virus leading to progressive multifocal leukoencephalopathy. These findings underscore the critical need for vigilant post-treatment monitoring for both immediate and delayed adverse reactions.

### *Ethical approval*

This study was conducted in full compliance with the ethical principles and national standards for conducting medical research in Iran. Ethical approval for the research was granted by the Research Ethics Committees of Tabriz University of Medical Sciences, under the approval ID IR.TBZMED.REC.1401.862, on December 19, 2022. The proposal was reviewed and approved by the Biomedical Research Ethics Committee, and it is the responsibility of the principal investigator (PI) and other collaborators to adhere to the legal and professional requirements outlined by the committee. Any modifications to the study protocol or documents must be reported to the committee as required. Prior to participation, informed consent was obtained from all patients, either in written or verbal form, depending on the nature of the interaction (in-person or via telephone follow-up). The confidentiality of patient data was ensured by anonymizing all personal information, and access to data was restricted to authorized research personnel only. All efforts were made to minimize risks to participants, including thorough pre-

treatment testing and follow-up evaluations to monitor for any adverse effects.

***Inclusion and exclusion criteria***

Patients were qualified for inclusion in the study if they had a confirmed diagnosis of pemphigus vulgaris, as evidenced by documentation in their medical records and verified by a dermatologist, and if they had been treated with Rituximab to improve the clinical course of PV. The study excluded individuals who had used Rituximab before the study began, those critically ill, pregnant, under 18 years of age, or diagnosed with conditions other than pemphigus vulgaris, including other autoimmune skin diseases. Also excluded were those treated with Rituximab at dosages diverging from the 500 mg per week protocol for up to one month, as well as those receiving Rituximab for indications other than pemphigus vulgaris.

Long-term complications, including hepatic dysfunction and cytopenia, were diagnosed based on standardized laboratory criteria and clinical guidelines. Hepatic dysfunction was confirmed using liver enzyme panels and imaging where applicable, while cytopenia was diagnosed according to defined thresholds for neutrophil and platelet counts in accordance with established hematologic standards. Any uncertain cases were further evaluated with additional testing or expert consultation to ensure diagnostic accuracy.

In instances of uncertainty regarding long-term complications, further information was sought through telephone contact, under the oversight of the ethics committee and the guiding professor (participants had the right to withhold any requested information). Calls that were not answered by the patient or their first-degree family members, or responses provided by individuals other than these, led to the exclusion of the related long-term complication data from the analysis.

We acknowledge the potential for recall bias inherent in retrospective interviews, and we took steps to minimize this by focusing on complications that were well-documented or still present at the time of the interview. Additionally, in cases where patients themselves were unavailable, responses were accepted from close family members, but these were corroborated with available medical records to ensure data accuracy.

To mitigate recall bias to the greatest extent possible, telephone inquiries about short-term complications were avoided, focusing instead on complications that emerged post-discharge or were still present at the time of the interview.

Laboratory data included results from both within and outside the center. For the diagnosis of PML, reliance was placed on images or reports from any type of brain imaging conducted for any reason, accessible for the study, either within or outside the center. It is pertinent to note that imaging represents the most practical diagnostic approach for PML.

***Method of administration***

Our cases routinely receive pre-treatment with intravenous chlorpheniramine and hydrocortisone, along with oral acetaminophen, to prevent hypersensitivity reactions prior to administering Rituximab. Rituximab is typically infused slowly over 3 hours with 500 mg in normal saline, under cardiac monitoring, and may be repeated weekly for up to a month as needed, with a re-evaluation after six months. Before initiating rituximab therapy, all patients underwent thorough pre-treatment testing, including a complete blood count (CBC) with differential, a purified protein derivative (PPD) test for tuberculosis screening, and, in some cases, a chest X-ray (CXR). Additionally, patients were tested for hepatitis B surface antigen (HBs Ag), anti-hepatitis B core antibody (Anti-HBc antibody), hepatitis C virus (HCV) antibody, and HIV antigen. These baseline assessments were conducted to ensure patient safety and screen for potential latent infections or hematological abnormalities that could be exacerbated by rituximab therapy.

***Data analysis***

The collected data were analyzed using SPSS software version 25. As this study was descriptive in nature, the analysis primarily focused on summarizing the characteristics of the study population and the incidence of adverse reactions. Descriptive statistics were used to present the data as follows:

*For Continuous Variables*

The mean, standard deviation, and range were calculated to describe variables such as patient age and the duration of rituximab treatment.

*For Categorical Variables*

Frequencies and percentages were calculated for variables such as gender, severity of pemphigus vulgaris, and the incidence of different adverse reactions.

*Presentation of Results*

The results were presented in tables and figures, providing an overview of the distribution of patient demographics, the frequency of adverse reactions, and the distribution of these reactions over time (e.g., according to infusion sessions).

*Data Integrity*

Where applicable, missing data points were noted, but their impact on overall findings was minimal, as the majority of key variables were well-documented in patient records

**Results**

During the four-year study period, our facility hospitalized 201 patients with a confirmed diagnosis of pemphigus vulgaris. A subset of 73 (36.3%) was managed with

Rituximab; within this group, 17 (23.3%) experienced side effects (Table 1). The participants' ages ranged from 25 to 73 years. Those on Rituximab had a mean age of 49.63 years, just under the overall average of 50.57 years. The gender distribution was similar across all patients, with Rituximab recipients being 41.1% male and 58.9% female, closely aligning with the full cohort's 42.8% male and 57.2% female. The individuals reporting side effects had a slightly lower mean age of 45.88 years, with a gender split of 41.2% male to 58.8% female. (Table 2)

### *Short term side effects*

The majority of short-term side effects were acute infusion-related reactions (Table 3), representing 82.4% of the adverse effects, equating to 19.17% of those treated with Rituximab. The incidence of adverse effects varied with the number of administrations; half of the adverse events occurred during the first infusion, 42.9% during the second, and 7.1% were reported during the fifth infusion (Table 4). Pruritus was the most common symptom, affecting 64.3% of those with side effects, and was effectively managed with supportive care. Chills and localized urticarial rashes each occurred in 21.4% of the affected patients, which resolved within a few hours without specific intervention. Additionally, signs of anaphylaxis, including hypotension, tachycardia, dyspnea, and tachypnea, were observed in 7.1% of the patients experiencing adverse reactions.

### *Long-term side effects*

In the evaluation of long-term side effects, feedback was obtained from 54 of the 73 patients who received Rituximab, with 12 responses from individuals other than the patients themselves. Long-term complications were reported by 5% of patients. Reactivation of Herpes Viruses was observed in two patients, a male and a female, with a mean age of 47.5 years, representing 50% of the late-onset adverse effects (Table 5). These cases were described as dermatomal zoster and labial herpes occurring within one month post-infusion. Hepatic dysfunction was reported by one 42-year-old female patient, constituting 25% of late-onset adverse effects. This presented with a cholestatic enzyme pattern and was confirmed to be drug-induced, with viral etiologies ruled out, within one month of infusion. Cytopenia was another condition, accounting for the remaining 25% of late complications, reported by a 52-year-old female patient.

In terms of severe neurological outcomes, neuroimaging for Progressive Multifocal Leukoencephalopathy (PML) was conducted in two patients during hospital stays unrelated to Rituximab therapy. The CT scans did not show patchy lesions that would be indicative of PML.

Moreover, it was noted that women were more frequently affected by Rituximab-related adverse effects than men, a trend that persisted across both acute and long-term complications. This gender-based disparity emphasizes the need for heightened awareness when monitoring potential side effects in female patients. Additionally, within the follow-up period, there were three instances of mortality; however, none were linked to known Rituximab-related adverse effects, suggesting an overall manageable safety profile for the medication.

## Discussion

In this study, we explored the prevalence and nature of rituximab-associated adverse effects in pemphigus vulgaris (PV), an autoimmune blistering disease characterized by severe dermatological manifestations. Given the historical

**Table 1.** gender and average age of patients

| | all patients | patients who received rituximab as a treatment for PV | Patients receiving rituximab who manifested with one or more adverse effects |
|---|---|---|---|
| number | 201 | 73 | 17 |
| average age | 50.75 | 49.63 | 45.88 |
| gender ratio | 42.8% male<br>57.2% female | 41.1% male<br>58.9% female | 41.2% male<br>58.8% female |

**Table 2.** Infusion related adverse effects occurrences in relation to gender

| | occurrence of adverse effect during infusion | no occurrence of adverse effect during infusion |
|---|---|---|
| male | 5 | 2 |
| female | 9 | 1 |

**Table 3.** Prevalence of different manifestations of infusion-related adverse effects

| Manifestation | Prevalence |
|---|---|
| itching | 64.3% |
| rashes | 21.4% |
| chills | 21.4% |
| anaphylaxis symptoms (tachycardia, tachypnea, hypotension, dyspnea) | 7.1% each |

**Table 4.** Prevalence of infusion related adverse effects regarding times of infusion

| | |
|---|---|
| **1st infusion** | 50% |
| **2nd infusion** | 42.9% |
| **3rd infusion or later** | 7.1% |

**Table 5.** Overview of age and gender distribution in patients who manifested with long term adverse effects

| Adverse effect | prevalence of patients who manifested with an adverse effect | number and gender of patients | average age |
|---|---|---|---|
| reactivation of herpes viridae | 50% | 1 male<br>1 female | 47.5 |
| drug-induced hepatic dysfunction | 25% | 1 female | 42 |
| cytopenia | 25% | 1 female | 52 |
| reactivation of viral hepatitis, primary or secondary infection with M. Tuberculosis, PML, SJS/TEN, long term cardiovascular adverse effects, etc. | 0% | no patients | - |

mortality rates significantly reduced by treatments like corticosteroids, rituximab's introduction has marked a pivotal advancement in PV management. Approved for moderate to severe cases, its targeted action against CD20 on B lymphocytes offers a promising therapeutic avenue, albeit with potential hypersensitivity and other side effects. This research aims to assess rituximab's safety profile, focusing on hypersensitivity reactions and their management, alongside investigating age and gender correlations in adverse responses among PV patients. Through this, we seek to contribute to the optimization of rituximab use, enhancing patient outcomes and minimizing risks.

***Early on-set adverse effects / Hypersensitivity reactions***

In randomized controlled trials, 80-90% of patients who were administered rituximab experienced allergic or anaphylactic conditions. These reactions typically occurred within 30 to 120 minutes after the primary infusion and ranged from minor to life-threatening.[22] According to a study by Min Cho et al., mild to moderate HSR following rituximab injection are relatively common, occurring in up to 77% of patients during the first infusion.[23] However, in our study, only 19.17% of patients experienced HSR post-injection, a figure lower than many studies, partly due to the pre-treatment prior to rituximab injection at this center.

Pre-treatment with antihistamines, acetaminophen, and corticosteroids is common for preventing infusion reactions for most monoclonal antibodies, without adversely affecting the drug's efficacy. A study by Jung et al. in 2014 on patients with B-cell malignancies evaluated the effect of pre-treatment with glucocorticoids for rituximab administration. The study noted a decrease in injection-related reactions, assessed at 2.7% in patients who received glucocorticoids, compared to 13% in those who did not.[24]

Regarding the impact of gender on HSR, a study by Fidanci et al. between 2015 and 2021 on 312 patients who showed allergies to various drugs, found no correlation between gender and drug allergies.[25] Similarly, according to a study by Salvati et al. in 2019, there seems to be no clear relationship between gender and anaphylaxis in adulthood, although anaphylaxis due to all causes (food allergens, drugs, etc.) is more common in boys during childhood.[26]

In our center's study, the incidence of HSR was higher in female patients compared to male, in both short and long-term adverse events, which could be attributed to the higher prevalence of female patients in our studied population (Table 6). Given the small number of cases, this finding cannot be generalized to the entire population. However, heightened susceptibility among female patients emphasizes the importance of gender-specific considerations in clinical practice.

We also examined the correlation between the adverse effects of rituximab and the ages of the recipients (Figure 1), drawing on research conducted by Lemoine et al. in France from 2006 to 2019, which analyzed 1096 instances of rituximab-related side effects. It was found that older patients were less likely to report injection-related side effects compared to other adverse effects.[27] Overall, data on rituximab's safety in elderly populations

**Table 6.** Age and gender distribution regarding both categories of adverse effects

| category | average age | gender ratios |
|---|---|---|
| infusion-related and short term adverse effects | 45.21 | 35.7% male<br>64.3% female |
| long term adverse effects | 47.25 | 25% male<br>75% female |

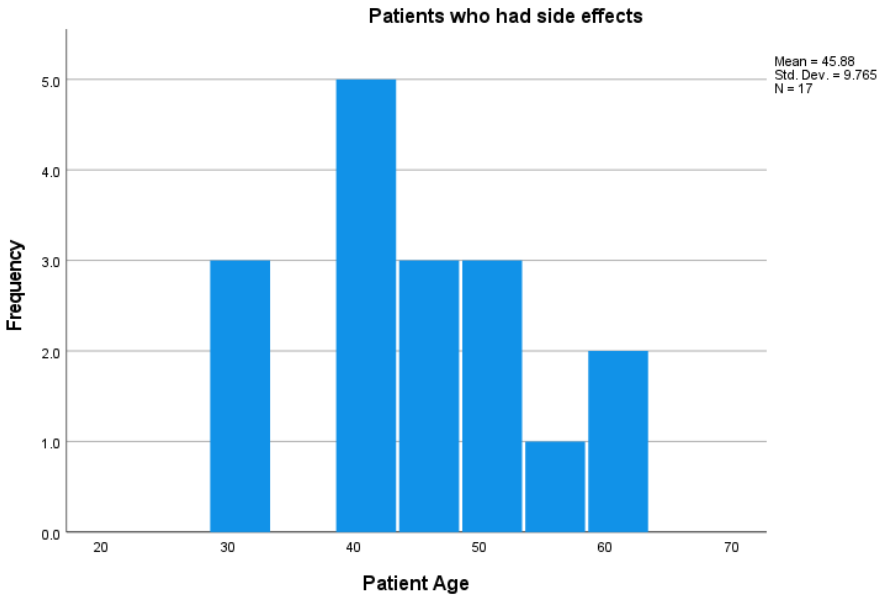


**Figure 1.** Age distribution in patients who manifested with infusion-related adverse effects

remain scarce, largely because the conditions it treats are more common in younger demographics. Additionally, a significant portion of older patients with oncological, rheumatological, and autoimmune diseases is precluded from rituximab therapy due to contraindications.

Contrary to previous findings, the current study's limited sample size precludes a broad conclusion about age and gender preferences in injection-related reactions. Within the confines of this study's demographic, those who exhibited acute reactions to rituximab were, on average, over four years younger than the mean age of all recipients (Figure 1). No notable gender difference was observed in the frequency of side effects among the patient group that reported at least one adverse effect, in comparison to the overall patient cohort.

Most injection-related adverse reactions were documented during the initial infusion, with a decline observed in subsequent sessions. The distribution of these reactions, according to the infusion sequence, is detailed in Table 1.

### *Late on-set adverse effects*

In our study, rituximab was associated with a variety of side effects beyond acute hypersensitivity reactions in the treatment of pemphigus vulgaris. Notably, long-term complications were reported by 5% of patients, highlighting the need for vigilance in post-treatment monitoring. These included reactivation of herpes viruses in two patients, indicative of possible viral susceptibility post-infusion, and hepatic dysfunction in one patient who manifested with cholestasis and elevated bilirubin levels three months subsequent to receiving their fourth infusion of rituximab. Such side effects are exceedingly rare, with few instances documented in the medical literature, and the underlying mechanisms remain poorly understood. Upon readmission for jaundice evaluation, the patient was diagnosed with drug-induced cholestasis attributed to rituximab, following the exclusion of alternative hepatic injury etiologies and the confirmation of negative viral markers.

Additionally, cytopenia was observed in another patient, reflecting potential hematological impacts. These findings, representing a spectrum of side effects ranging from infectious reactivations to organ-specific toxicity, underscore the importance of comprehensive safety assessments after rituximab therapy.

Another noteworthy finding of this study is the absence of any cases of latent tuberculosis (TB) reactivation. It is important to mention that none of the patients exhibited evidence of latent TB in pre-treatment screenings. This aligns with the majority of research on the relationship between rituximab administration and TB incidence, which suggests that TB infections are more commonly associated with the use of anti-TNF monoclonal antibodies, whereas rituximab is more frequently linked to atypical mycobacterial infections.[28]

### Limitations

One of the study's limitations is the omission of an analysis on type III hypersensitivity reactions, with serum sickness being the primary concern. Serum sickness typically initiates at least one week post-administration, with its classic triad of symptoms (fever, skin rash, and joint pain) manifesting in approximately 45% of rituximab-associated serum sickness cases.[29] The decision to exclude this complication from the study was influenced by the clinical presentation's heterogeneity. Many manifestations, such as arthralgia and myalgia, are non-specific and can easily be confounded with symptoms resulting from musculoskeletal injuries or acute viral infections. Additionally, the potential influence of recall bias further complicated the assessment of this adverse reaction.

Most studies have not demonstrated a significant difference in the efficacy or safety profiles between prominent rituximab brands, such as MabThera and Reditux. Due to the absence of specific brand documentation in the patient records at Sina Treatment Center, the analysis did not differentiate between the brands in terms of their potential to cause adverse effects. Limited data were available on patients' pre-administration medication storage practices, both from telephone interviews and medical records. A study by Saavedra et al. highlighted that 20% of patients lacked awareness of the importance of maintaining the pharmaceutical cold chain.[30] Considering the relevance of these findings to the Sina Treatment Center's cohort, it is imperative to prioritize patient education on proper drug storage post-purchase and to investigate the implications of inadequate storage on treatment outcomes through retrospective analysis in future studies.

## Conclusion

This comprehensive study examined the prevalence and nature of rituximab-associated adverse effects in pemphigus vulgaris (PV) patients, highlighting the necessity for rigorous monitoring of both immediate and delayed reactions post-treatment. While rituximab has shown efficacy in managing pemphigus vulgaris, conclusions about its overall safety profile should be drawn with caution. The limitations in capturing long-term complications, including the relatively small sample size, highlight the need for larger, prospective studies to better assess the full scope of rituximab's safety profile. This investigation underlines the importance of personalized patient care and continuous monitoring to optimize treatment outcomes and minimize risks associated with rituximab therapy in PV.

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**Competing Interests**

The authors state no conflicts of interest regarding this study. They have not received any financial support or compensation related to this research.

**Data Sharing**

The supporting data for this study's findings can be obtained from the corresponding author upon a justified request. These data are subject to restrictions due to their use under license for the current research and are not publicly accessible because of privacy and ethical considerations. For any queries related to the data sharing policy, please reach out to the corresponding author.

**Ethical Approval**

This research was conducted in strict compliance with ethical standards, securing written informed consent from all participants or their legal representatives. To ensure patient confidentiality, all identifiable information was anonymized and stored securely. Approval for the study was granted by the ethics committee of the Tabriz University of Medical Sciences, under the approval number IR.TBZMED.REC.1401.862. Data integrity was upheld through uniform data collection methods and the independent verification of adverse effects

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