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Varicella-Zoster Virus Infection-Associated Venous Thromboembolism: A Descriptive Review of 55 Cases

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Abstract

Background

Varicella-zoster virus (VZV) infection is typically self-limiting, but in rare cases, it can be complicated by venous thromboembolism (VTE), including cerebral venous sinus thrombosis (CVST), deep vein thrombosis (DVT), and pulmonary embolism (PE). Currently, systematic summaries regarding its clinical characteristics, thrombophilia background, and prognosis are relatively limited.

Methods

We searched PubMed and China National Knowledge Infrastructure (CNKI) databases for reports and case series of confirmed cases from the establishment of the databases to April 2026. These documents were required to meet both criteria: a clearly diagnosed VZV infection (primary varicella, herpes zoster, or herpes zoster without rash) and imaging-confirmed VTE. Afterwards, we used descriptive statistical methods to summarize the demographic characteristics of patients, types of VZV infection, locations of thrombosis, results of thrombophilia testing, treatment strategies, and prognosis.

Results

We included a total of 47 articles, encompassing 55 patients. The average age was 33.8 ± 22.6 years, with 67.3% being male and 70.9% having primary varicella. The average interval from rash onset to thrombus formation was 10.7 ± 5.3 days. Isolated CVST was the most common manifestation (40.0%), while multi-site thrombosis accounted for 27.3%. Among the 29 patients who completed thrombophilia testing, transient abnormalities (transient antiphospholipid antibodies and/or temporary reductions in protein S/C) accounted for 44.8%, genetic abnormalities accounted for 10.3%, and mixed abnormalities accounted for 10.3%. Antiviral combined with antithrombotic therapy was the main treatment strategy (58.2%). At discharge, 29.1% of patients achieved complete recovery, 63.6% achieved complete recovery requiring prophylactic treatment, and the overall good outcome rate was 92.7%, with no deaths. During follow-up (information available for 37 patients), the incidence of sequelae was 16.2%, predominantly post-thrombotic syndrome.

Conclusions

VZV-associated VTE primarily affects young males. Isolated CVST is the most common manifestation. Its core mechanism is closely related to the transient hypercoagulable state induced by the virus. Antiviral combined with antithrombotic therapy can lead to a good prognosis, but long-term sequelae cannot be ignored. Clinicians should maintain high vigilance, promptly identify and treat this complication.

1 Background

Varicella-zoster virus (VZV) is a highly neurotropic double-stranded DNA virus. Humans are its only natural host. Primary infection causes chickenpox, after which the virus becomes latent in the ganglia. When cellular immunity decreases, the virus can be reactivated, leading to herpes zoster [1]. Although VZV infection is generally considered to be self-limiting, increasing evidence suggests that it is closely associated with various thrombotic events, including cerebral venous sinus thrombosis (CVST), deep vein thrombosis (DVT), and pulmonary embolism (PE) [2].

The underlying mechanism of thrombosis following VZV infection is complex and not fully elucidated. Viral-induced coagulopathy is not unique to VZV; for example, influenza virus, HIV, CMV, and various hemorrhagic fever viruses can also affect different aspects of the coagulation system, exhibiting a tendency towards thrombosis or hemorrhage [3]. The current mainstream view is that the transient hypercoagulable state induced by the virus plays a central role in this process. VZV infection can trigger the production of autoantibodies such as antiphospholipid antibodies and anti-protein S antibodies, leading to a temporary decrease in protein S or protein C activity and thereby disrupting the coagulation–anticoagulation balance [4]. In addition, direct viral injury to the vascular endothelium and secondary inflammatory storms (e.g., elevated cytokines IL-6 and TNF-α) further activate the coagulation cascade and promote thrombosis [2].

Nagel et al. explicitly stated in their review of VZV vasculopathy that VZV infection can involve cerebral arteries, venous sinuses, and peripheral vessels, causing a range of thrombotic complications including CVST, DVT, and peripheral thrombosis, and that approximately one-third of patients have no preceding rash [1]. A recent review by Livieratos et al. further summarized the epidemiology, pathological mechanisms, and treatment advances of VZV-related stroke, emphasizing that the risk of stroke is significantly increased in the short term after VZV reactivation and that antiviral therapy combined with corticosteroids may be effective in some patients [5].

However, systematic summaries specifically targeting VZV-associated thrombosis are still limited. Most of the evidence comes from case reports or small case series, lacking a comprehensive analysis of the patients' clinical characteristics, thrombus types, thrombophilia background (especially the distinction between transient and genetic factors), treatment strategies and long-term outcomes.

2 Methods

Study design, setting, and aim

This article is a systematic descriptive review of published case reports and case series. The purpose of this study was to systematically review the published cases of VZV-associated thrombosis, and summarize their clinical epidemiological characteristics, spectrum of thrombotic events, laboratory abnormalities (especially thrombophilia), treatment patterns and outcomes, so as to improve clinicians' understanding of thrombotic complications after VZV infection, and provide references for early identification and optimal management.

Search strategy

We systematically searched PubMed and CNKI for VTE literature related to VZV infection from March to April 2026. The searched strategy combines subject words and free words, used Chinese and English keywords, and focused on the following two concept groups:

1. VZV infection-related: herpes zoster, varicella zoster virus, VZV;
2. Venous thromboembolism-related: venous thromboembolism, deep vein thrombosis, pulmonary embolism, cerebral venous thrombosis, cerebral venous sinus thrombosis, portal vein thrombosis, mesenteric vein thrombosis, splanchnic vein thrombosis.

The search was conducted from the establishment of the database to April 2026, with language restrictions set to Chinese and English. We also manually screened the reference lists of the included literature to identify any potentially omitted studies.

Inclusion and exclusion criteria

2.1.2 Inclusion criteria
Study type: case reports or case series, regardless of sample size.

Population: patients diagnosed with VZV infection (serological or PCR evidence is required for herpes zoster without rash).

Thrombotic event: imaging-confirmed VTE (e.g., CT venography, MRI/MRV, Doppler ultrasound, CT pulmonary angiography), including CVST, DVT, PE, splanchnic vein thrombosis (e.g., portal or mesenteric veins), and venous thrombosis at other sites.

Data integrity: articles must report at least the core information (age, sex, thrombus location, treatment, and outcome at discharge or follow-up) to support descriptive data extraction.
2.1.3 Exclusion criteria
Non-venous thrombotic events: arterial stroke without accompanying venous thrombosis, or thrombosis site unclear/suspected only.

Confounding etiology: thrombosis clearly attributable to another dominant cause (e.g., bacterial infection, prolonged immobility, active malignancy) or the temporal association with VZV infection is unclear (such as thrombosis occurring several months after rash onset).

Severely incomplete information: conference abstracts, letters, or other document types that lack key clinical data for effective data extraction.

Duplicate or overlapping data: the same patient is reported in multiple articles – only those with more complete reports are included.

Language: non-English or non-Chinese publications.

Data extraction

The authors did the data extraction on their own. To cut down on bias and make sure things were accurate, we did a second round of extraction more than a week later, then compared each item with the first round. If anything didn't match, we went back to the original articles to sort it out. The variables we pulled covered six main areas:

1. Basic bibliographic information: first author, publication year.
2. Patient demographic and VZV infection characteristics: age, sex, VZV infection type (primary varicella, herpes zoster, zoster sine herpete), interval from rash to thrombosis.
3. Thrombus characteristics: site of thrombosis (CVST, DVT, PE, splanchnic veins, etc.), classification of multi-site thrombosis.
4. Diagnostic and laboratory findings: VZV serology and cerebrospinal fluid (CSF) results; thrombophilia markers (protein S, protein C, antiphospholipid antibodies, factor V Leiden, etc.).
5. Treatment measures: antiviral drugs, antithrombotic therapy (anticoagulation and thrombolysis), and classification of treatment strategies.
6. Outcome measures: outcome at discharge, follow up outcome, and duration of follow up.

A detailed variable extraction checklist is provided in the Appendix.

Analytical strategy

All the studies we included were case reports or case series, so the evidence level is low. In addition, the cases varied considerably — including differences in age, type of VZV infection, clot location, treatment regimen, and follow-up duration. That means traditional meta-analysis or inferential stats (like t-tests, chi-square tests, or regression) didn't make sense here. We just used descriptive statistics to sum up and present the data. All analyses were done with Microsoft Excel 2021.

2.1.4 Continuous variables

For age (years) and the interval from rash to thrombosis (days), data are presented as mean ± standard deviation (Mean ± SD). Other laboratory parameters (e.g., D-dimer, protein S, protein C) were not subjected to central tendency analysis because of varied testing methods, different normal ranges, and substantial missing data; only the ranges or specific values reported in the original articles are described.

2.1.5 Categorical variables

Categorical variables are presented as frequencies (n) and percentages (%). The percentage is figured out by taking the number of cases that actually had a clear record for that variable as the bottom number (denominator). We note this in the tables.

2.1.6 Subgroup descriptive comparisons

We split the cases into subgroups based on the clinical questions we wanted to look at, then did some descriptive comparisons. No hypothesis testing was done, and we didn't calculate any P-values. We just describe potential trends that the differences in percentages or means might hint at. Because some subgroups have pretty small sample sizes, the comparison results are only descriptive clues — so take them with caution and don't overinterpret.

1. 1.By VZV infection type: primary varicella (n = 39) vs. herpes zoster (n = 11) vs. zoster sine herpete (n = 5). Comparisons included thrombus location distribution, thrombophilia test results, and outcomes (at discharge and follow up).
2. 2.By treatment strategy: antithrombotic therapy alone (n = 19) vs. antiviral plus antithrombotic therapy (n = 31) vs. thrombolysis plus antithrombotic therapy without antivirals (n = 3). Comparisons included outcomes (at discharge and follow up).

2.1.7 Handling of missing data

If a variable didn't have complete information, we didn't guess or fill in anything — we just reported the data we actually had. We put “not reported” or “unknown” in the tables, and we also talk about how the missing data might have affected things.

3 Results

Literature search results

We got 276 articles from PubMed (166) and CNKI (110). After taking out duplicates, 198 were left. We screened by title and abstract and removed papers that weren't on topic or weren't case reports or case series, which left 69. Then we did full-text screening on those 69, plus we manually checked their reference lists and found 5 more eligible articles. That gave us 74 articles going into formal full-text screening. After applying our inclusion and exclusion criteria, we excluded 23 articles. The reasons were: the clot type was arterial stroke or myelitis without venous thrombosis, the clot diagnosis was unclear or only suspected, there were clear confounding factors, or the information was too incomplete. Ultimately, 47 articles were included, comprising 38 case reports and 9 case series (from which only individual cases meeting the venous thrombosis diagnosis were extracted), encompassing a total of 55 patients who developed venous thromboembolism following varicella-zoster virus infection [6–52]. The details of the selection process are shown in Fig. 1.

Baseline patient characteristics

The baseline characteristics of the 55 patients are shown in Table 1. Males accounted for 67.3%, and primary varicella was the most common type of infection (70.9%).

Table 1
Summary of baseline patient characteristics

Characteristic	Number (N = 55)	Percentage / Mean ± SD
Age (years), mean ± SD	55	33.79 ± 22.62
Age group		
Children (< 18 years)	16	29.1%
Adults (18–60 years)	30	54.5%
Elderly (> 60 years)	9	16.4%
Sex		
Male	37	67.3%
Female	18	32.7%
VZV infection type		
Primary varicella	39	70.9%
Herpes zoster	11	20.0%
Zoster sine herpete	5	9.1%
Rash-to-thrombosis interval (days, N = 37), mean ± SD	37	10.73 ± 5.34
Note: Detailed patient bibliographic information and baseline characteristics (first author, publication year, age, sex, VZV infection type, etc.) are provided in Supplementary Table 1.		
Thrombus characteristics		

The distribution of thrombus sites among the 55 patients is presented in Table 2. Isolated CVST was the most common (40.0%), and multi-site thrombosis accounted for 27.3%.

Table 2
Distribution of thrombus sites (mutually exclusive categories)

Thrombus site category	Number (N = 55)	Percentage
CVST only	22	40.0%
DVT only	12	21.8%
PE only	5	9.1%
Other only	1	1.8%
Multi-site thrombosis (CVST + DVT+PE, etc.)	15	27.3%
Note: Detailed thrombus event characteristics for each patient (rash to thrombosis interval, specific thrombus sites, multi site classification, etc.) are provided in Supplementary Table 2.		
Thrombophilia testing results		

Among the 29 patients for whom thrombophilia test results were reported, transient abnormalities (antiphospholipid antibodies and/or temporary reductions in protein S/C) accounted for 44.8%, while no abnormalities were found in 34.5% (Table 3).

Treatment strategies

The distribution of treatment strategies among the 55 patients is shown in Table 4. Antiviral plus antithrombotic therapy was the most commonly used strategy (58.2%), while antithrombotic therapy alone was used in 32.7%.

Table 3
Distribution of thrombophilia test results (N = 29)

Type of thrombophilia abnormality	Number (N = 29)	Percentage of tested cases
Transient abnormality	13	44.8%
Hereditary abnormality	3	10.3%
Mixed abnormality	3	10.3%
No abnormality	10	34.5%
Note: Detailed laboratory and thrombophilia results for each patient (VZV serology, CSF testing, protein S/C, antiphospholipid antibodies, etc.) are provided in Supplementary Table 3.		

Table 4
Distribution of treatment strategies

Treatment strategy	Number (N = 55)	Percentage
No treatment	1	1.8%
Antiviral only	1	1.8%
Antithrombotic only	18	32.7%
Antiviral + antithrombotic	32	58.2%
Thrombolysis + antithrombotic (without antiviral)	3	5.5%
Note: Detailed treatment strategies and anticoagulation regimens (antiviral drugs, antithrombotic agents, thrombolysis, anticoagulant type and duration) for each patient are provided in Supplementary Table 4.		
Outcomes		

At discharge, 92.7% of patients achieved complete recovery (including those requiring preventive treatment), and no deaths occurred. During follow-up (information available for 37 patients), the incidence of sequelae was 16.2% (Table 5).

Table 5
Outcome distribution at discharge and at follow-up

Outcome grade	At discharge (N = 55)	At follow-up (N = 37)
Complete recovery	16 (29.1%)	15 (40.5%)
Complete recovery (requiring preventive treatment)	35 (63.6%)	15 (40.5%)
Partial recovery	4 (7.3%)	1 (2.7%)
Sequelae	0	6 (16.2%)
Death	0	0
Lost to follow-up	—	18 (32.7%)
Note: Outcome grade definitions: Complete recovery = no symptoms/signs, no treatment needed; Complete recovery (preventive) = no functional deficit but requires long term anticoagulation/antiepileptic therapy; Partial recovery = mild functional impairment not affecting daily life; Sequelae = significant functional impairment requiring ongoing rehabilitation/care; Death. Percentages at follow up are calculated using the 37 patients with follow up information as the denominator; the lost to follow up rate is calculated based on the total 55 patients. Detailed discharge and follow up outcomes for each patient (status at discharge, follow up results, sequelae, etc.) are provided in Supplementary Table 5.		
Subgroup comparisons		

3.1.1 VZV infection type and thrombus site

Stratified analysis of thrombus site distribution by VZV infection type is shown in Table 6. Among patients with primary varicella (n = 39), CVST only was the most frequent (41.0%). Due to small sample sizes, the distributions for herpes zoster and zoster sine herpete are presented descriptively in Table 6.

Table 6
VZV infection type and thrombus site (mutually exclusive categories)

VZV type	Total N	CVST only	DVT only	PE only	Other only	Multi-site
Primary varicella	39	16 (41.0%)	11 (28.2%)	2 (5.1%)	0	10 (25.6%)
Herpes zoster	11	4 (36.4%)	1 (9.1%)	1 (9.1%)	1 (9.1%)	4 (36.4%)
Zoster sine herpete	5	2 (40.0%)	0	2 (40.0%)	0	1 (20.0%)
Total	55	22 (40.0%)	12 (21.8%)	5 (9.1%)	1 (1.8%)	15 (27.3%)

3.1.2 VZV infection type and thrombophilia test results

Among the 29 patients with thrombophilia test results, the distribution of abnormalities by VZV infection type is shown in Table 7. Because only a few patients with herpes zoster or zoster sine herpete underwent testing, their results are listed only descriptively.

Table 7
VZV infection type and thrombophilia test results (tested cases only)

VZV type	Tested N	Transient abnormality	Hereditary abnormality	Mixed abnormality	No abnormality
Primary varicella	26	12 (46.2%)	3 (11.5%)	3 (11.5%)	8 (30.8%)
Herpes zoster	1	1 (100%)	0	0	0
Zoster sine herpete	2	0	0	0	2 (100%)

3.1.3 VZV infection type and outcomes

Outcome distributions at discharge and at follow-up are shown in Table 8. Given the small sample sizes for herpes zoster and zoster sine herpete, the outcome proportions should be interpreted with caution.

Table 8
VZV infection type and outcomes (at discharge and follow-up)

VZV type	Time point	Complete recovery	Complete recovery (preventive)	Partial recovery	Sequelae	Death	Lost to follow-up
Primary varicella	Discharge (N = 39)	13 (33.3%)	24 (61.5%)	2 (5.1%)	0	0	—
	Follow-up (N = 28)	12 (42.9%)	13 (46.4%)	1 (3.6%)	2 (7.1%)	0	11 (28.2%)
Herpes zoster	Discharge (N = 11)	1 (9.1%)	9 (81.8%)	1 (9.1%)	0	0	—
	Follow-up (N = 6)	1 (16.7%)	2 (33.3%)	0	3 (50.0%)	0	5 (45.5%)
Zoster sine herpete	Discharge (N = 5)	2 (40.0%)	2 (40.0%)	1 (20.0%)	0	0	—
	Follow-up (N = 3)	2 (66.7%)	0	0	1 (33.3%)	0	2 (40.0%)

3.1.4 VZV Treatment strategy and outcomes

Outcomes at discharge and at follow up stratified by treatment strategy are shown in Table 9. Follow up data for the thrombolysis + antithrombotic group (3 patients) and the antithrombotic only group (19 patients) should be interpreted with caution because of small sample sizes.

Table 9
Treatment strategy and outcomes (at discharge and follow-up)

Treatment strategy	Time point	Complete recovery	Complete recovery (preventive)	Partial recovery	Sequelae	Death	Lost to follow-up
Antithrombotic only	Discharge (N = 19)	5 (26.3%)	13 (68.4%)	1 (5.3%)	0	0	—
	Follow-up (N = 12)	3 (25.0%)	6 (50.0%)	0	3 (25.0%)	0	7 (36.8%)
Antiviral + antithrombotic	Discharge (N = 31)	11 (35.5%)	19 (61.3%)	1 (3.2%)	0	0	—
	Follow-up (N = 22)	12 (54.5%)	9 (40.9%)	1 (4.5%)	0	0	9 (29.0%)
Thrombolysis + antithrombotic	Discharge (N = 3)	0	2 (66.7%)	1 (33.3%)	0	0	—
	Follow-up (N = 2)	0	0	0	2 (100%)	0	1 (33.3%)

4 Discussion

This systematic descriptive analysis of 55 cases of VTE following VZV infection from 47 articles comprehensively summarizes the clinical characteristics, thrombus types, thrombophilia background, treatment strategies, and outcomes of these patients. The main findings include: the patients were mainly young men, the most common type of infection was primary varicella, and the most common manifestation of thrombosis was isolated CVST. Nearly half of the patients who received thrombophilia testing had transient thrombophilia abnormalities (transient presence of antiphospholipid antibodies and/or temporary reductions in protein S/C). The most commonly used treatment strategy was antiviral combined with antithrombotic therapy. More than 90% of patients achieved complete recovery (including patients requiring preventive treatment) at discharge, but the incidence of sequelae was 16.2% in 37 patients with follow-up information.

Clinical features of VZV-associated thrombosis

In this study, the average age of patients was 33.8 years, and 67.3% were male. This indicates that VZV-associated thrombosis mainly affects young men, consistent with earlier reports [1, 2]. The main type of infection was primary varicella (70.9%), which may be because primary varicella is common and VZV-specific cellular immunity is not fully established in children at the time of primary infection. Postherpetic thrombus accounted for about 20%, and most of these patients were elderly (average age 68 years), which was consistent with the known law: with age, VZV-specific immunity declines, making virus reactivation more common [1]. Herpes zoster without rash accounted for only 9.1%. However, its thrombotic risk cannot be ignored. Among these 5 patients, 3 cases had multi-site thrombosis or pulmonary embolism. Livieratos et al. [5] pointed out that about one-third of patients with VZV vasculopathy had no rash before. The low proportion of non-eruptive cases in this study may be due to the fact that the diagnosis of such cases relies on VZV serology or cerebrospinal fluid PCR, which makes it difficult to identify clinically, thus failing to fully reflect the true incidence of non-eruptive VZV thrombus.

When observing the site of thrombosis, isolated CVST was the most common (40.0%), while all cases involving CVST accounted for 67.3%. This is consistent with what Nagel et al. said in their review [1]: VZV vascular lesions can involve cerebral venous sinus, and the virus spreads from trigeminal ganglion or superior cervical ganglion to dural venous sinus along nerve fibers, thus triggering local thrombosis. In addition, multi-site thrombosis accounted for 27.3%. This indicates that VZV infection can cause systemic hypercoagulability, which is not limited to a certain group of vessels.

Central role of transient hypercoagulable state

Among the 29 patients who were tested for thrombophilia, transient abnormalities accounted for 44.8%. If mixed anomalies are included, the proportion is more than half. This strongly supports the view that VZV infection causes thrombosis by inducing a transient hypercoagulable state.

The transient hypercoagulable state induced by the virus is not unique to VZV. A systematic review by Goeijenbier et al. [3] pointed out that many viruses (such as influenza virus, HIV and CMV) can activate the coagulation cascade through common pathways, including stimulating inflammatory cytokines, reducing natural anticoagulant proteins and blocking the fibrinolytic system. The case-control study of Ferrara et al.

[4] provided direct evidence for the mechanism of VZV specificity. They compared three groups of children: varicella with thrombosis group (Group I), uncomplicated varicella group (Group II) and healthy control group (Group III). The results showed that the levels of protein C (61.38%) and free protein S (45.70%) in group I were significantly lower than those in groups II and III. In addition, the positive rates of lupus anticoagulant, antiphospholipid antibody and anti protein S antibody were significantly increased (all $P < 0.05$). At the same time, group II (varicella patients without thrombosis) also had some coagulation abnormalities (protein C 88.76%, protein S 80.75%), but to a lesser extent. This indicates that VZV infection itself can trigger the production of autoantibodies, but the actual thrombosis will occur only when the antibody level is high enough or there are other genetic risk factors.

A review by Zerangian et al. [2] also clarified the mechanism behind VZV-associated thrombosis: the virus directly invades the vascular wall and damages the endothelium; transient autoantibodies lead to acquired protein S deficiency; inflammatory factors activate the coagulation system. In our study, three cases showed mixed abnormalities. This is consistent with the "second-hit" hypothesis, where VZV infection, as an acquired trigger, significantly increases the risk of thrombosis when superimposed on genetic thrombophilia (such as the factor V Leiden mutation or inherited protein S/C deficiency).

A recent study by Bubak et al. [53] found a new mechanism by which VZV causes thrombosis. They found that plasma exosomes from patients with herpes zoster carried a variety of prothrombotic proteins (such as coagulation factors V and XIII). These proteins can significantly activate platelets, manifested by increased P-selectin and phosphatidylserine, and also promote platelet-leukocyte aggregation. This prothrombotic effect persists for three months after herpes zoster, which explains why the thrombotic risk remains elevated for some time after VZV infection. This finding is also consistent with what we observed in this study: the incidence of sequelae during follow-up was 16.2%. This suggests that the virus-triggered prothrombotic factors in the blood may still play a role even after the rash subsides.

Treatment strategies and outcomes

In this study, antiviral plus antithrombotic therapy was the most commonly used strategy (58.2%), and in this group the rate of complete recovery (including those requiring preventive treatment) at discharge was as high as 96.8%, and remained at 95.5% at follow-up, with no sequelae. In contrast, the thrombolysis + antithrombotic (without antiviral) group had only 3 cases, with a complete recovery rate of 66.7% at discharge, and both cases with follow-up progressed to sequelae; the antithrombotic-only group had a sequelae rate of 25.0% at follow-up. These data suggest that combination antiviral therapy may be important for improving long-term outcomes.

Nagel et al. [1] provided clear treatment recommendations for VZV vascular lesions. For patients with normal immune function, they recommended intravenous acyclovir (10–15 mg/kg, three times daily) for 14 days, accompanied by anticoagulant therapy for venous thrombosis. There is also epidemiological evidence supporting the early use of antiviral drugs. A review by Yawn et al. [54] summarized several studies and found that the risk of stroke after herpes zoster was significantly increased, especially within the first month, and timely antiviral treatment may reduce this risk. Livieratos et al. [5] further discussed

additional treatment. For severe VZV vascular disease, the addition of glucocorticoids may help reduce the inflammation of the vascular wall, but the risk of immunosuppression should be cautioned. In addition, herpes zoster vaccines (especially recombinant subunit vaccines) can reduce the risk of post-herpetic stroke. Our own observational data are consistent with these recommendations, suggesting that antiviral therapy not only clears the virus and blocks immune triggers, but also may reduce the duration of transient autoantibody production, thereby reducing the recurrence rate and sequelae.

The overall prognosis at discharge was good, with 92.7% achieving complete recovery (including patients requiring preventive treatment) and no deaths reported, which was consistent with the conclusions of most case reports. However, during the follow-up period, the incidence of sequelae increased to 16.2%, including post-thrombotic syndrome (limb swelling, valve problems) and some neurological problems. This suggests that despite the low mortality in the acute phase, long-term functional problems cannot be ignored. The incidence of sequelae was higher in the herpes zoster group (50%) and the herpes zoster without rash group (33.3%), which may be related to older age, more comorbidities, or delayed diagnosis.

Comparison with HIV cohort studies

Fiordelisi et al. [55] conducted a retrospective cohort study involving 581 HIV-infected individuals and found that a history of herpes zoster was associated with an increased risk of ischemic events (myocardial infarction, stroke, and limb thrombosis) (odds ratio [OR] 3.14, 95% confidence interval [CI] 1.12–7.68). In this HIV population, the increase in stroke risk after VZV reactivation was particularly significant (OR 5.71). Although our study did not include HIV patients, their study still supports the view that VZV infection is a trigger of vascular events from another perspective. It should be noted that HIV-infected individuals inherently have chronic inflammation and a hypercoagulable state. When VZV reactivates, this is compounded by transient increases in antiphospholipid antibodies and decreases in protein S, forming a "second-hit" scenario. In our study, patients with mixed abnormalities (transient combined with genetic) had more widespread thrombosis and poorer prognosis, which is consistent with the "second-hit" model.

Limitations

This study has several limitations. Firstly, all the studies we included were case reports and case series, which implies publication bias; and there was a lack of control group, thus making it impossible to calculate the incidence rate or relative risk. Secondly, there were significant differences in diagnostic criteria, laboratory methods, treatment regimens, and follow-up durations among the cases; due to incomplete data, some variables, such as the exact normal range of D-dimer or protein S/C, could not be quantitatively combined. Thirdly, only 52.7% of the cases underwent testing for thrombophilia, and the testing methods used varied among cases, which may have led us to underestimate the actual prevalence of hereditary thrombophilia. Fourthly, the high rate of loss to follow-up (32.7%) may affect our assessment of long-term outcomes. Lastly, this study is a descriptive review, and all comparisons are descriptive analyses without verification through hypothesis testing. Therefore, conclusions should be interpreted with caution.

5 Conclusion

This is the first systematic descriptive review that pulls together clinical and thrombophilia data from published case reports and case series on VZV-related venous thromboembolism. Here's what we found. VZV-associated clots mostly affect young males (average age 33.8 years, 67.3% male). Primary varicella is the most common infection type (70.9%), and the average time from rash to clot is about 10.7 days. Isolated cerebral venous sinus thrombosis shows up most often (40.0%), and about one quarter of patients have clots in multiple places — which points to a virus-caused system-wide hypercoagulable state. Nearly half of those who got tested had transient thrombophilia abnormalities (antiphospholipid antibodies and/or temporary drops in protein S/C), and some had hereditary factors on top of that. That backs up the “two-hit” idea. The main treatment strategy was antivirals plus antithrombotic (58.2%). At discharge, over 90% had complete recovery (including those who needed preventive treatment), and no one died. But during follow-up, sequelae — mostly post-thrombotic syndrome — happened in about 16% of patients. So in short, VZV infection is a rare but important trigger for venous thromboembolism, working through a temporary hypercoagulable state. Clinicians need to stay alert. If a patient has headache, limb swelling, or trouble breathing after a VZV infection, they should promptly screen for clots and start combined antiviral and antithrombotic therapy.

Abbreviations

VZV
Varicella-zoster virus
VTE
venous thromboembolism
CVST
cerebral venous sinus thrombosis
DVT
deep vein thrombosis
PE
pulmonary embolism
CNKI
China National Knowledge Infrastructure
CSF
cerebrospinal fluid

Declarations

Ethics statement

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Consent for publication

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Author Contribution

H.S. and J.Z. contributed equally to this work.H.S.: conceptualization, data curation, formal analysis, investigation, writing – original draft, writing – review and editing. J.Z.: conceptualization, writing – review and editing. Y.Z.: conceptualization, methodology, supervision, writing – review and editing. All authors reviewed and approved the final manuscript.

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Data Availability

All data generated or analyzed during this study are included in this published article and its supplementary information files. The original case reports and case series included in this review are publicly available in PubMed and CNKI databases as cited in the reference list.

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Figures

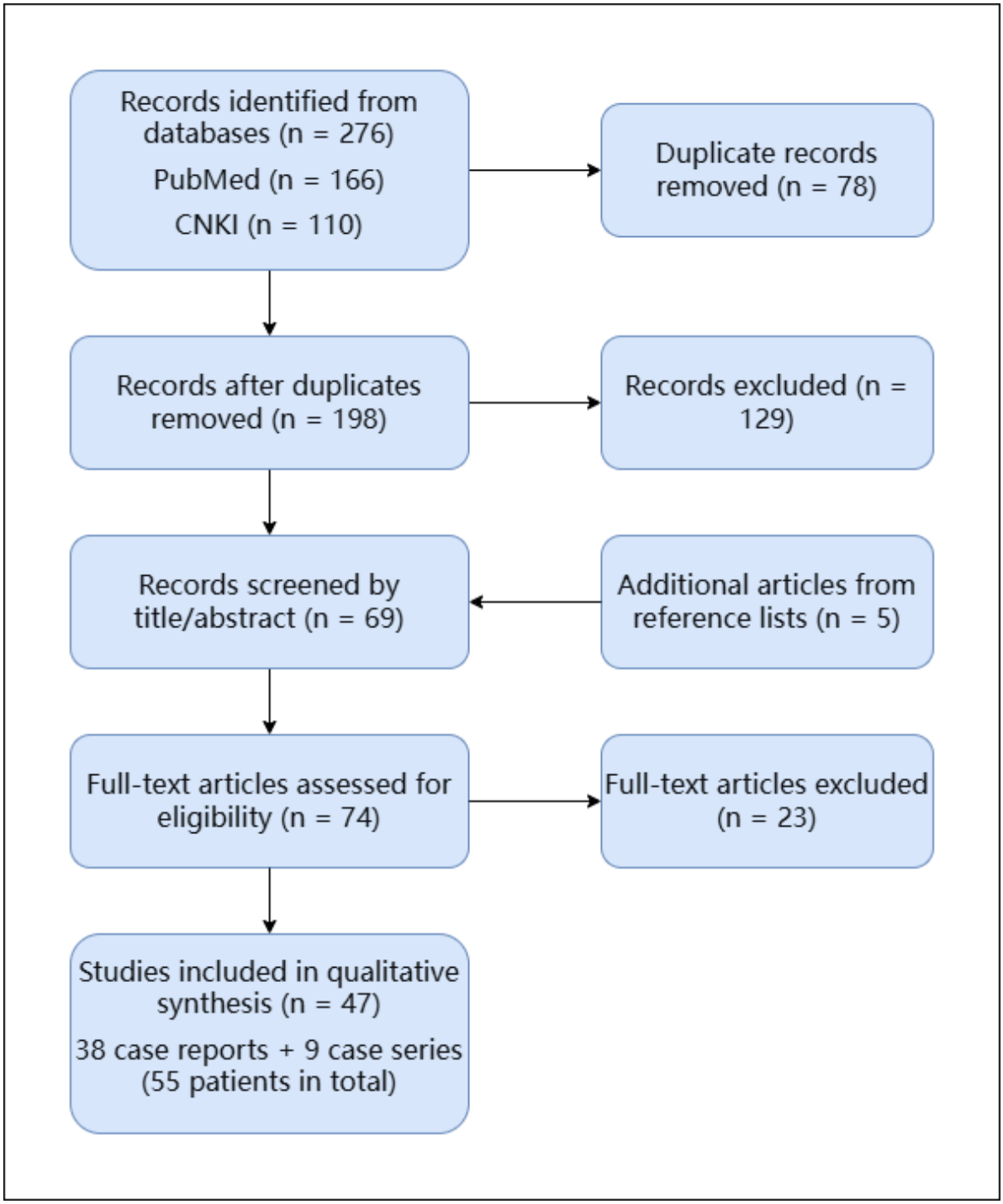


Figure 1

PRISMA flow diagram of study identification and selection

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