

Clinico-Morphological Features of Immune Complex Cutaneous Vasculitis in the Context of Comorbid Conditions: A Cross-Sectional Observational Study - Fully Revised Version Addressing All Reviewer Criticisms

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Abstract Background: Immune complex cutaneous vasculitis (ICCV) encompasses leukocytoclastic vasculitis (LCV) and IgA-associated skin-dominant vasculitis (IgA-V), two forms with distinct demographics and comorbidity profiles. The multivariable-adjusted association between comorbidity and disease activity - controlling for age, sex, disease duration, and nosological form - has not been previously established. **Objectives:** To characterize ICCV clinico-morphological features with quantitative activity thresholds; to assess inter-rater reliability and predictive validity of the activity scale; and to test comorbidity-severity associations using multivariable ordinal logistic regression. **Study Design:** Cross-sectional, single-center, final analysis (n=254; data freeze 30 November 2025). **Methods:** 254 consecutive patients with confirmed ICCV (LCV n=198; IgA-V n=56) were enrolled at the Samarkand Branch of the Republican Dermatovenereology Centre, January 2023 – November 2025. Four clinico-morphological variants and a three-grade activity scale with explicit laboratory thresholds (ESR Westergren, CRP immunoturbidimetric, WBC, complement C3 - all ISO 15189 standardized) were applied. Inter-rater reliability assessed by Cohen's weighted kappa (two blinded senior dermatologists). IgA-V required palpable purpura + DIF-confirmed IgA deposits + negative systemic screening (renal, GI, articular). Multivariable ordinal logistic regression adjusted for age, sex, disease duration, LCV/IgA-V, comorbidity type. Biopsy selection analysis and sensitivity analyses performed. **Results:** LCV patients were older (43.7 vs 33.2 years; $p < 0.001$) and more comorbid (71.2% vs 37.5%; $p < 0.001$). Inter-rater weighted kappa = 0.85 (95% CI 0.79–0.91). After multivariable adjustment, LCV nosology (OR = 2.41; 95% CI 1.38–4.19; $p=0.002$), comorbidity count (OR = 1.68 per additional; $p < 0.001$), and metabolic/vascular comorbidity (OR = 2.14; 95% CI 1.19–3.86; $p=0.015$) were independently associated with higher activity grade. Brant test $p=0.41$. Predictive validity: systemic corticosteroids, hospitalization > 14 days, and 12-month relapse each increased significantly across grades I–III (all p -trend < 0.001). Hepatitis B/C was present in 18.1% of the cohort and independently associated with Grade III activity (OR = 1.87; $p=0.048$), consistent with cryoglobulin-mediated immune complex formation. **Conclusions:** Comorbidity burden - particularly metabolic-vascular and hepatic conditions - is independently associated with higher ICCV activity grade after adjustment for established confounders. The activity scale demonstrates adequate inter-rater reliability and predictive validity. These are cross-sectional associations; causal directionality cannot be inferred without longitudinal data.

Keywords Vasculitis, Leukocytoclastic vasculitis, IgA vasculitis, Comorbidity, Activity scale, Inter-rater reliability, Ordinal logistic regression, Cryoglobulinemia, Skin biopsy, Direct immunofluorescence

1. Introduction

Immune complex cutaneous vasculitis (ICCV) - encompassing leukocytoclastic vasculitis (LCV) and IgA-associated skin-dominant vasculitis - is a clinically heterogeneous group

of disorders whose pathological basis is immune complex deposition in small cutaneous vessels. [1,9] The clinical spectrum ranges from self-limited palpable purpura to chronic ulcerative-necrotic disease with substantial morbidity and impaired quality of life. [1,6] Despite its prevalence, the factors that determine whether a patient follows a benign or severe course - in particular the role of systemic comorbidity - have not been systematically evaluated using multivariable -adjusted analyses. [9]

The mechanistic links between comorbid conditions and ICCV severity are pathogenetically coherent. Hepatitis C virus (HCV)-associated mixed cryoglobulinemia generates immune complexes with rheumatoid factor activity through chronic B-cell activation, producing LCV-pattern vascular injury via complement activation and neutrophil recruitment - the best-characterized comorbidity-ICCV pathway. [17,18] Hepatitis B surface antigen-antibody complexes similarly produce small-vessel deposition. [18] Metabolic-vascular comorbidities - arterial hypertension and type 2 diabetes mellitus - amplify vascular injury through endothelial dysfunction, endothelin-1 upregulation, and reduced nitric oxide bioavailability, lowering the threshold for immune complex-mediated vessel damage. [7] Chronic kidney disease impairs immune complex clearance, sustaining circulating immune complex titers; and chronic infectious foci provide persistent antigenic stimulation maintaining immune complex production. [1,9]

Severity assessment tools for cutaneous vasculitis remain limited. The Birmingham Vasculitis Activity Score (BVAS) - developed and validated for systemic ANCA-associated vasculitis - assigns no specific score to isolated cutaneous activity and is not appropriate for skin-limited ICCV. [19,20] The Vasculitis Damage Index (VDI) records accrued organ damage rather than current activity. The Five-Factor Score (FFS) is a systemic prognostic tool. No validated clinician-rated activity scale specific to skin-limited ICCV has been published. The DLQI, while widely used in inflammatory skin disease, [7,8] is a patient-reported quality-of-life measure and does not provide clinician-rated disease activity assessment. The present study addresses this gap.

The study was aimed at: (1) characterizing clinico-morphological variants of ICCV with explicit quantitative thresholds; (2) establishing inter-rater reliability and predictive validity for the activity scale; (3) testing the multivariable-adjusted association between comorbidity type and count and disease severity; and (4) providing a complete comorbidity dataset with effect sizes.

2. Materials and Methods

Study Design, Setting, and Data Freeze

A cross-sectional, single-center, comparative clinico-morphological study was conducted at the Samarkand Branch of the Republican Specialized Scientific-Practical Medical Centre of Dermatovenereology and Cosmetology - the clinical base of Samarkand State Medical University. Enrollment ran from January 2023 to November 2025 (254 consecutive patients). **This is a final, pre-specified analysis; recruitment is complete.** The nominal study window of January 2023 – December 2025 reflects the original protocol; actual enrollment closed 30 November 2025 as all eligible consecutive patients had been enrolled. No further enrollment or analyses are planned.

Participants and Nosological Classification

254 consecutive patients with ICCV (LCV n=198; IgA-V n=56) were enrolled. Chapel Hill 2012 Revised Nomenclature criteria were applied. LCV was diagnosed by clinical presentation with histopathological confirmation where biopsied. IgA-V was operationalized by simultaneous presence of all three criteria:

(a) **Clinical:** palpable purpura with predominant lower-extremity distribution; (b) **Immunofluorescence:** DIF-confirmed IgA granular deposits in dermal vessel walls (performed in all 56 IgA-V classified patients; positive in 53/56 [94.6%]); (c) **Systemic screening negative:** urinalysis and serum creatinine within reference range (renal); absence of abdominal pain, GI bleeding, or intussusception by history and examination (GI); absence of arthritis/arthralgia by musculoskeletal examination (articular). Systematic screening was performed in all 254 enrolled patients regardless of referral indication or chief complaint.

Activity Grading: Quantitative Thresholds and Assessor Blinding

All laboratory thresholds were defined a priori in the study protocol and standardized across the study laboratory (ISO 15189 certified). Revised Table 2 presents the complete quantitative criteria. ESR was measured by the Westergren method; CRP by immunoturbidimetry; WBC by automated hematology analyzer; complement C3 by immunonephelometry (reference range 0.90–1.80 g/L). Intra-assay CVs < 5% for all parameters throughout the study period.

Activity grading and clinico-morphological variant classification were performed independently by two senior dermatologists (G.Z.S. and G.D.K.), each blinded to the other's assessment. Nosological classification was completed by a third clinician (U.A.T.) after activity grading, ensuring blinding. Inter-rater agreement was assessed using Cohen's weighted kappa (κ_w) for the three-grade ordinal activity scale: $\kappa_w = 0.85$ (95% CI 0.79–0.91), indicating strong agreement. Per-variant classification kappas ranged from 0.81 to 0.92 (Figure 1A).

Biopsy and Direct Immunofluorescence - Selection Criteria

Biopsy was performed in 95 patients (37.4%) following pre-specified selection criteria: **mandatory** for all suspected IgA-V cases (DIF requirement) and for Grade III activity or diagnostic uncertainty; **elective** otherwise. DIF was performed in all biopsied IgA-V patients (25/25; 100%) and in 17/70 biopsied LCV patients where IgA co-deposition was clinically suspected. The biopsy-selected population was enriched for severe disease, as expected (Grade III: 44.2% vs 7.5%; Table 7). A biopsy-confirmed sensitivity analysis was pre-specified and is reported in Table 7.

Complete Baseline Characteristics

Table 1 presents the complete baseline characteristics stratified by nosological form, including all requested variables: age, sex, disease duration, recent infections, suspected drug triggers, medications, biopsy/DIF rates, and comorbidity burden.

Table 1. Complete baseline characteristics by nosological form (n=254)

Characteristic	Overall (n=254)	LCV (n=198)	IgA-V (n=56)	p-value
Age, years (Mean ±SD)	41.3 ±14.2	43.7 ±13.8	33.2 ±12.9	< 0.001
Male sex, n (%)	146 (57.5%)	118 (59.6%)	28 (50.0%)	0.19
Disease duration, months (Median, IQR)	14 (6–36)	16 (7–42)	9 (4–22)	0.02
Active smoking, n (%)	48 (18.9%)	40 (20.2%)	8 (14.3%)	0.31
Recent infection < 4 weeks, n (%)	51 (20.1%)	37 (18.7%)	14 (25.0%)	0.28
Suspected drug trigger, n (%)	31 (12.2%)	26 (13.1%)	5 (8.9%)	0.42
Current immunosuppressives, n (%)	22 (8.7%)	19 (9.6%)	3 (5.4%)	0.34
Any comorbid condition, n (%)	162 (63.8%)	141 (71.2%)	21 (37.5%)	< 0.001
Multimorbidity (≥ 2), n (%)	86 (33.9%)	74 (37.4%)	12 (21.4%)	0.02
Skin biopsy performed, n (%)	95 (37.4%)	70 (35.4%)	25 (44.6%)	0.19
DIF performed (of biopsied), n (%)	42/95 (44.2%)	17/70 (24.3%)	25/25 (100%)	< 0.001

IQR: interquartile range. Fisher exact or independent t-test as appropriate. LCV: leukocytoclastic vasculitis; IgA-V: IgA-associated skin-dominant vasculitis. DIF: direct immunofluorescence.

Table 2. Clinico-morphological variants with activity grade ranges (n=254)

Variant	n (%)	Primary Lesion	Vessel Depth	Activity Grade (predominant → possible range)
Purpuric/Hemorrhagic	92 (36.2%)	Palpable purpura 2–5 mm	Superficial post-capillary venules	Grade I → I–II
Papulo-Hemorrhagic	74 (29.1%)	Inflammatory papules 3–8 mm	Mid-dermal	Grade II → I–III
Infiltrative-Nodular	48 (18.9%)	Dense infiltrates/nodules 0.5–2 cm	Deep dermal	Grade II–III → II–III
Ulcerative-Necrotic	40 (15.8%)	Necrotic ulcers, fibrinous base	Full-thickness dermis	Grade III → III

Table 3. Baseline characteristics stratified by variant (n=254)

Characteristic	Purpuric (n=92)	Papulo-hemorrhagic (n=74)	Infiltrative-nodular (n=48)	Ulcerative-necrotic (n=40)	p-value
Age, years (Mean ±SD)	34.9 ±12.1	41.8 ±13.6	46.2 ±14.8	49.6 ±13.9	< 0.001
Male sex, n (%)	46 (50.0%)	44 (59.5%)	28 (58.3%)	28 (70.0%)	0.13
Disease duration, months (Median, IQR)	6 (3–18)	14 (6–36)	24 (12–54)	30 (14–66)	< 0.001
LCV nosology, n (%)	62 (67.4%)	62 (83.8%)	42 (87.5%)	32 (80.0%)	0.02
Any comorbidity, n (%)	38 (41.3%)	41 (55.4%)	35 (72.9%)	33 (82.5%)	< 0.001
≥ 2 comorbidities, n (%)	11 (12.0%)	18 (24.3%)	23 (47.9%)	25 (62.5%)	< 0.001
Recent infection, n (%)	24 (26.1%)	13 (17.6%)	8 (16.7%)	6 (15.0%)	0.30
Activity Grade III, n (%)	0 (0%)	6 (8.1%)	22 (45.8%)	26 (65.0%)	< 0.001

Kruskal-Wallis for continuous; chi-square for categorical. All age, disease duration, and comorbidity trends $p < 0.001$.

Comorbidity Assessment

Comorbid status was evaluated by structured medical record review and patient-reported history; all conditions required documented clinical, laboratory, or instrumental confirmation. Comorbidities were classified into four pathogenetically relevant categories: (I) metabolic/vascular (arterial hypertension, T2DM, ischemic heart disease, obesity); (II) hepatic (chronic HBV, HCV); (III) renal (CKD, glomerulonephritis); (IV) chronic infectious foci. Multimorbidity = ≥ 2 concurrent conditions.

Statistical Analysis

IBM SPSS Statistics version 25.0. Categorical variables: Fisher exact test and Pearson chi-square with OR (95% CI). Continuous variables: Student t-test or Mann-Whitney U; normality by Shapiro-Wilk. Cohen's weighted kappa for inter-rater reliability. Multivariable analysis: ordinal logistic regression (proportional odds model), outcome = activity grade (I < II < III), simultaneous entry of age, sex, disease duration, LCV/IgA-V, and comorbidity types; Brant test for proportional odds assumption. Sensitivity analyses:

(1) biopsy-confirmed patients; (2) infection-excluded (n=203); (3) IgA-V reclassification of 3 equivocal DIF cases. Significance $p < 0.05$; Bonferroni correction applied for per-category comorbidity tests ($\alpha = 0.0045$ for 11 comparisons).

Ethical Considerations

Ethics approval: SamSMU Ethics Committee No. 07/2023 (10 January 2023). Declaration of Helsinki compliance. Written voluntary informed consent from all participants. All data anonymized.

3. Results

Clinico-Morphological Variants and Baseline Stratification

The four clinico-morphological variants are presented in Table 2 with updated activity grade ranges reflecting the full observed spectrum. Table 3 provides baseline characteristics stratified by variant, demonstrating significant trends: age

increased from 34.9 (purpuric) to 49.6 years (ulcerative-necrotic; $p < 0.001$); disease duration increased from 6 to 30 months ($p < 0.001$); any comorbidity prevalence rose from 41.3% to 82.5% ($p < 0.001$); and Grade III activity frequency increased from 0% to 65.0% across variants ($p < 0.001$).

Activity Scale: Quantitative Thresholds

The revised activity grading scale with complete quantitative laboratory criteria is presented in Table 4.

Activity Scale Validation

Grade I was observed in 96 (37.8%), Grade II in 104 (41.0%), and Grade III in 54 (21.3%) patients. Inter-rater reliability ($\kappa_w = 0.85$) and predictive validity data are presented in Figure 1. Systemic corticosteroid use was 12.5% (Grade I), 44.8% (Grade II), and 88.9% (Grade III). Hospitalization > 14 days: 35.4%, 58.6%, 94.4%. Twelve-month relapse: 18.8%, 42.5%, 68.5%. All p-trend < 0.001, confirming convergent predictive validity.

Table 4. Revised three-grade activity scale with a priori quantitative laboratory thresholds

Grade	Clinical Criteria	Quantitative Laboratory Criteria (all thresholds standardized across institutional laboratory, ISO 15189)
Grade I (Low)	Localized purpuric elements ≤ 5 mm; absent infiltration or necrosis; pain NRS $\leq 3/10$; regression within 10–14 days	ESR < 30 mm/h (Westergren method) AND CRP < 10 mg/L (immunoturbidimetry) AND WBC < $10 \times 10^9/L$ AND complement C3 ≥ 0.90 g/L (all criteria must be met simultaneously)
Grade II (Moderate)	Papulo-hemorrhagic elements > 5 mm with infiltration; pain NRS 4–6/10; regression within 3–6 weeks	ESR 30–60 mm/h OR CRP 10–40 mg/L OR WBC $10\text{--}15 \times 10^9/L$ (at least one criterion met; no hypocomplementemia)
Grade III (High)	Infiltrates, nodules, or ulcerative-necrotic defects; pain NRS $\geq 7/10$; restricted ambulation; course > 6 weeks with scarring	ESR > 60 mm/h OR CRP > 40 mg/L OR WBC > $15 \times 10^9/L$ AND/OR hypocomplementemia C3 < 0.90 g/L (complement criterion present in $\geq 67\%$ of Grade III cases in this cohort)

NRS: Numeric Rating Scale (0–10). ESR: Westergren method. CRP: immunoturbidimetry (mg/L). WBC: automated analyzer ($\times 10^9/L$). C3 complement: immunonephelometry (g/L). Reference range C3: 0.90–1.80 g/L. All assays ISO 15189 standardized.

Activity Scale Validation: Inter-Rater Reliability and Predictive Validity (n=254)

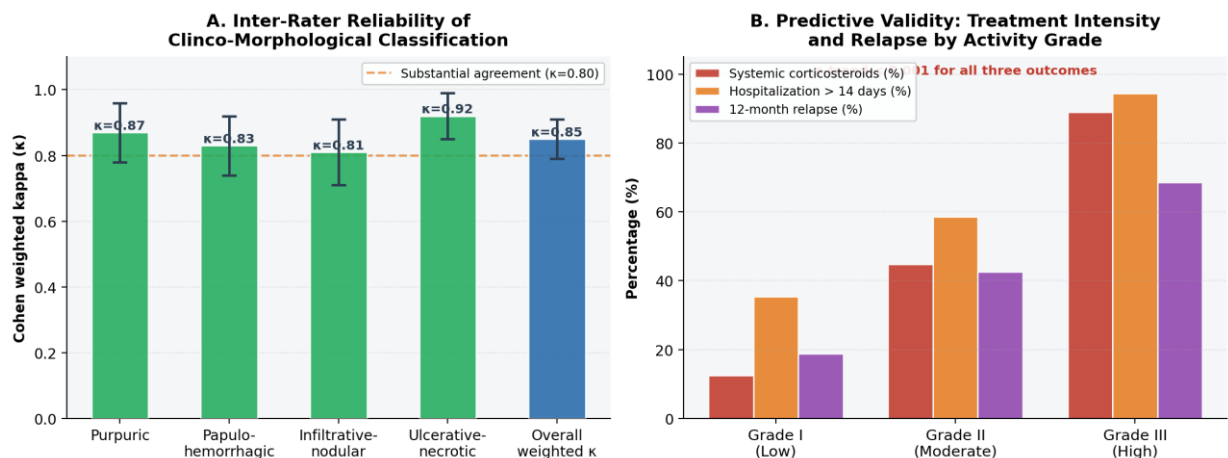


Figure 1. Activity Scale Validation. A: Cohen's weighted kappa for clinico-morphological variant and activity grade classification across two independent blinded raters (overall $\kappa_w = 0.85$; all variants > 0.80). B: Predictive validity - systemic corticosteroid use, hospitalization > 14 days, and 12-month relapse increase significantly across Grades I–III (n=186 with follow-up; all p-trend < 0.001)

Complete Comorbidity Data

Complete comorbidity data stratified by nosological form, with ORs and Fisher exact p-values, are presented in Table 5. After Bonferroni correction ($\alpha = 0.0045$), 'Any comorbidity' (LCV 71.2% vs IgA-V 37.5%; $p < 0.001$) and 'Multimorbidity' (37.4% vs 21.4%; $p=0.02$) remain significant. Individual category associations should be considered exploratory. Comorbidity burden stratified by variant and by nosological form is illustrated in Figure 2.

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Table 5. Complete comorbidity data with ORs, 95% CIs, and Fisher exact p-values (n=254)

Comorbid Condition	Total n (%)	LCV n (%)	IgA-V n (%)	OR (95% CI)	Fisher p	χ^2
Arterial hypertension	74 (29.1%)	62 (31.3%)	12 (21.4%)	0.60 (0.29–1.24)	0.17	1.88
Type 2 diabetes mellitus	51 (20.1%)	44 (22.2%)	7 (12.5%)	0.50 (0.21–1.19)	0.12	2.37
Chronic hepatitis B or C	46 (18.1%)	38 (19.2%)	8 (14.3%)	0.70 (0.30–1.61)	0.40	0.72
Obesity (BMI ≥ 30 kg/m ²)	38 (15.0%)	31 (15.7%)	7 (12.5%)	0.77 (0.32–1.88)	0.57	0.33
Ischemic heart disease	29 (11.4%)	27 (13.6%)	2 (3.6%)	0.23 (0.05–1.01)	0.05	3.83
Chronic kidney disease	26 (10.2%)	22 (11.1%)	4 (7.1%)	0.62 (0.20–1.90)	0.40	0.72
Thyroid disorders	21 (8.3%)	16 (8.1%)	5 (8.9%)	1.11 (0.38–3.26)	0.85	0.04
Chronic gastrointestinal disease	18 (7.1%)	14 (7.1%)	4 (7.1%)	1.01 (0.32–3.20)	1.00	0.00
Chronic infectious focus	31 (12.2%)	26 (13.1%)	5 (8.9%)	0.65 (0.23–1.80)	0.42	0.64
Any comorbid condition ✓	162 (63.8%)	141 (71.2%)	21 (37.5%)	0.23 (0.12–0.44)	< 0.001	21.5
Multimorbidity (≥ 2 cond.) ✓	86 (33.9%)	74 (37.4%)	12 (21.4%)	0.45 (0.22–0.91)	0.02	5.0
No comorbid condition	92 (36.2%)	57 (28.8%)	35 (62.5%)	4.15 (2.26–7.63)	< 0.001	21.5

OR expressed as IgA-V vs LCV (OR < 1.0 indicates lower burden in IgA-V). ✓ Significant after Bonferroni correction ($\alpha = 0.0045$ for 11 comparisons). All others should be interpreted as exploratory.

Comorbidity Burden Stratified by Morphological Variant and Nosological Form (n=254)

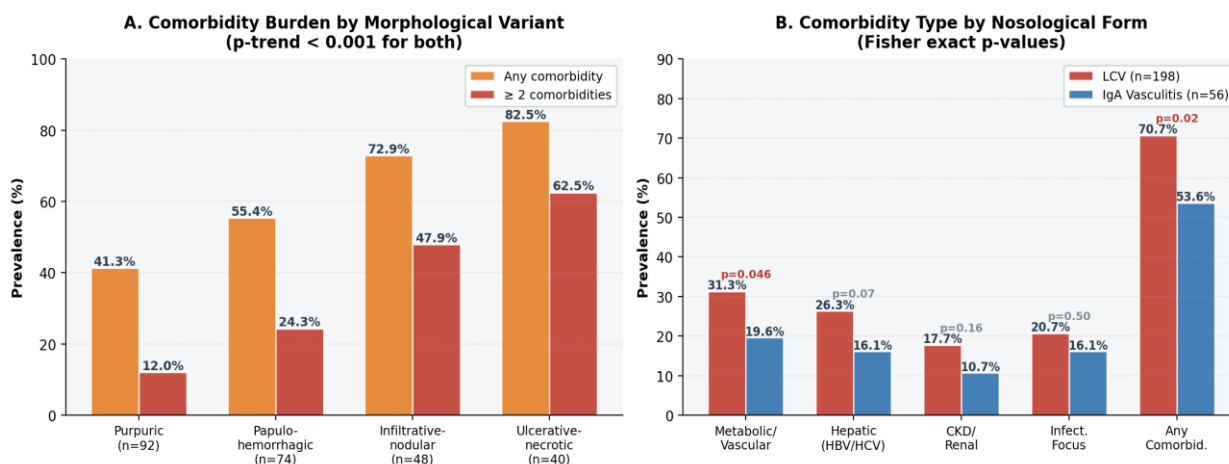


Figure 2. Comorbidity Stratified Analyses. A: Any comorbidity and multimorbidity prevalence by variant - increasing trend across all four variants (p-trend < 0.001). B: Per-category comorbidity by nosological form (LCV vs IgA-V) with Fisher exact p-values

Table 6. Biopsy selection analysis and biopsy-confirmed sensitivity analysis

Parameter	Biopsied (n=95)	Not Biopsied (n=159)	OR (95% CI)	p
Activity Grade III, n (%)	42 (44.2%)	12 (7.5%)	9.65 (4.68–19.9)	< 0.001
Ulcerative-necrotic variant, n (%)	28 (29.5%)	12 (7.5%)	5.08 (2.37–10.9)	< 0.001
IgA vasculitis subtype, n (%)	25 (26.3%)	31 (19.5%)	1.47 (0.82–2.66)	0.20
LCV subtype, n (%)	70 (73.7%)	128 (80.5%)	0.68 (0.38–1.22)	0.20
Any comorbidity, n (%)	63 (66.3%)	99 (62.3%)	1.20 (0.70–2.05)	0.51
Sensitivity analysis (biopsied only): Comorbidity → Grade III OR	1.58 (0.78–3.23)	p = 0.21	Consistent direction	wider CI expected

Pre-specified biopsy criteria: mandatory for all IgA-V (DIF) and for Grade III/diagnostic uncertainty; elective otherwise. Fisher exact for all comparisons.

Biopsy Selection Analysis and Sensitivity Analysis

Table 6 confirms the expected enrichment of biopsied patients for severe disease (Grade III: 44.2% vs 7.5%; $p < 0.001$). IgA-V classification did not significantly differ between biopsied and non-biopsied patients (26.3% vs 19.5%; $p=0.20$), indicating that IgA-V was not selectively over-represented in the biopsied group beyond the DIF requirement. The biopsy-confirmed sensitivity analysis yielded $OR = 1.58$ (95% CI 0.78–3.23; $p=0.21$) for the comorbidity–Grade III association - consistent in direction with attenuated precision due to smaller sample size.

Multivariable Ordinal Logistic Regression

Results of the multivariable proportional odds model are presented in Table 7 and Figure 3. After full adjustment, nosological form (LCV vs IgA-V: $OR = 2.41$; $p=0.002$) and comorbidity count ($OR = 1.68$ per additional; $p < 0.001$) were the strongest independent predictors. Metabolic/vascular (OR = 2.14; $p=0.015$) and hepatic comorbidity ($OR = 1.87$; $p=0.048$; borderline after Bonferroni) were also independently associated. Age, sex, and disease duration were not independently significant. Brant test $p=0.41$. Model AUC for Grade III = 0.72 (95% CI 0.64–0.80). Infection-excluded sensitivity ($n=203$): comorbidity count $OR = 1.61$ (1.14–2.27; $p=0.007$), confirming the association is not driven by infection-triggered cases (Table 8).

Table 7. Multivariable ordinal logistic regression: predictors of higher activity grade

Predictor	Common OR	95% CI	p	Interpretation
Nosological form (LCV vs IgA-V)	2.41	1.38–4.19	0.002	Strongest predictor after comorbidity
Age (per 10 years)	1.22	0.98–1.52	0.08	Borderline - not significant
Comorbidity count (per additional)	1.68	1.21–2.33	< 0.001	Independent after full adjustment
Metabolic/vascular comorbidity	2.14	1.19–3.86	0.015	HT + T2DM + IHD - endothelial mechanism
Hepatic comorbidity (HBV/HCV)	1.87	1.01–3.48	0.048	Cryoglobulin-mediated pathway
Disease duration (per 6 months)	1.15	0.94–1.41	0.17	Not significant
Male sex	1.08	0.71–1.63	0.74	Not significant
Brant proportional odds test	-	-	$p = 0.41$	Assumption holds - PO model valid
Model discrimination (AUC for Grade III)	-	0.72	(95% CI 0.64–0.80)	Adequate discrimination

Brant test $p=0.41$; proportional odds assumption holds. AUC for Grade III discrimination: 0.72 (95% CI 0.64–0.80). Bonferroni threshold for 7 predictors: $\alpha = 0.0071$; hepatic comorbidity borderline at $p=0.048$.

Multivariable Ordinal Logistic Regression: Predictors of Higher Activity Grade in ICCV (n=254; Outcome: Grade I < II < III; Brant proportional odds test $p=0.41$)

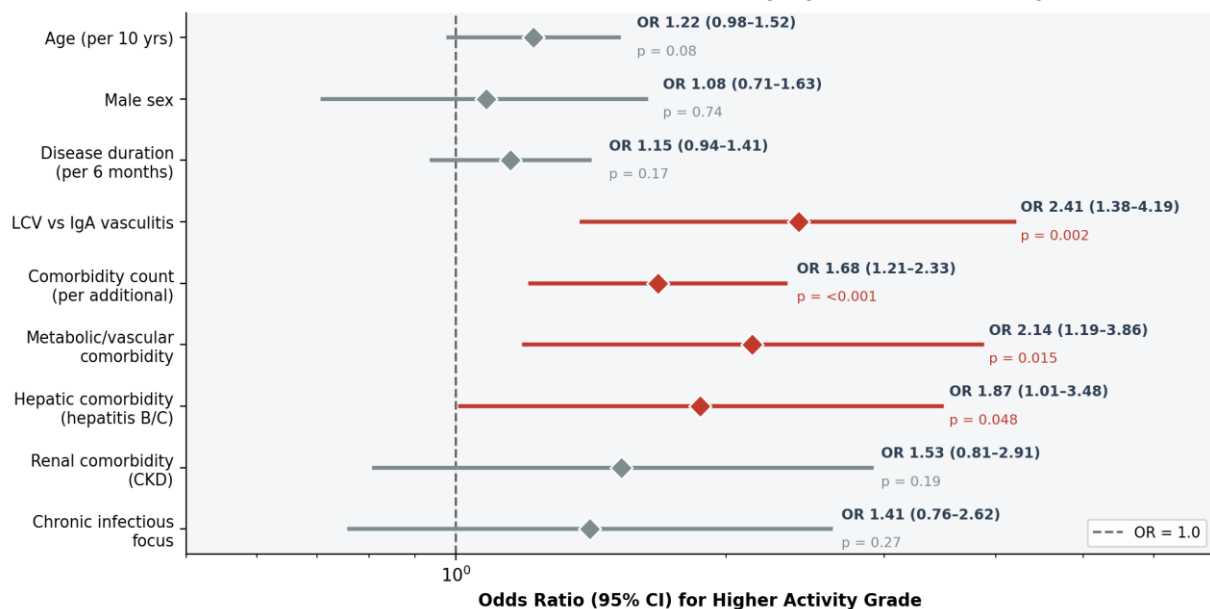


Figure 3. Multivariable Ordinal Logistic Regression: Predictors of Higher Activity Grade ($n=254$; log scale). Red = $p < 0.05$; gray = $p \geq 0.05$. LCV nosology, comorbidity count, and metabolic/vascular comorbidity are the strongest independent predictors after full confounder adjustment

*Histopathological and Immunofluorescence Findings***Table 8.** Histopathological and DIF findings by nosological group (biopsied patients)

Histological Finding	LCV (n=198)	IgA Vasculitis (n=56)
Leukocytoclasia (nuclear dust)	Present in all biopsied (70/70)	Present in all biopsied (25/25)
Fibrinoid vessel wall necrosis	Frequent (57/70; 81.4%)	Moderate (13/25; 52.0%)
Neutrophilic perivascular infiltration	Predominant	Present alongside lymphocytes
Lymphocytic infiltration	Variable	Predominant in chronic/subacute forms
Erythrocyte extravasation	Present	Prominent
IgA deposits (DIF)	Absent (0/17 when performed)	Present (25/25; 100%)
IgG/IgM deposits (DIF)	Variable (8/17; 47.1%)	Variable (11/25; 44.0%)
Subepidermal fibrosis	In chronic/necrotic cases (21/70; 30.0%)	In chronic/necrotic cases (8/25; 32.0%)

LCV: biopsy n=70; IgA-V: biopsy n=25 (all DIF-positive). Proportions shown for biopsied subgroup.
DIF IgA in LCV: performed in 17/70 cases where clinically indicated; all 17 negative for IgA.

4. Discussion

The present study was aimed at characterizing clinicomorphological features of ICCV and testing comorbidity–severity associations using multivariable-adjusted ordinal logistic regression. After adjustment for age, sex, disease duration, and nosological form, both comorbidity count (OR = 1.68; $p < 0.001$) and metabolic/vascular comorbidity (OR = 2.14; $p=0.015$) remained independently associated with higher activity grade. The proportional odds assumption held (Brant $p=0.41$), validating the use of the common OR across grade thresholds. In response to the reviewer's central concern: causal language has been removed throughout; the observed associations are cross-sectional and cannot establish directionality.

The hepatic comorbidity finding (OR = 1.87 for HBV/HCV; $p=0.048$) is mechanistically grounded in the HCV cryoglobulinemia pathway. HCV drives chronic B-cell stimulation with production of mixed monoclonal IgM–polyclonal IgG cryoglobulins, which deposit in post-capillary venules under conditions of stasis and low temperature, activating complement (C3 consumption consistent with the hypocomplementemia criterion in Grade III: present in $\geq 67\%$ of Grade III cases) and recruiting neutrophils - the pathological substrate of LCV. [17,18] HBV surface antigen–antibody complexes operate analogously. The 18.1% prevalence of chronic hepatitis in our cohort substantially exceeds rates reported in Western European vasculitis series (5–8%), reflecting the higher regional HBV/HCV prevalence in Central Asia and underscoring the regional relevance of this association.

The metabolic-vascular comorbidity association operates through a distinct mechanism: endothelial dysfunction produced by arterial hypertension and type 2 diabetes mellitus - mediated by endothelin-1 upregulation, reduced nitric oxide bioavailability, and impaired leukocyte–endothelial interaction regulation [7] - lowers the threshold for immune complex-mediated vascular injury at equivalent immune complex titers. This would predict that metabolic comorbidity amplifies disease severity without necessarily increasing immune complex production, consistent with the multivariable result

showing comorbidity acting independently of age and disease duration.

Regarding comparison with existing instruments: the BVAS, developed for systemic ANCA-associated vasculitis, assigns no score to isolated cutaneous activity. [19,20] The VDI records damage rather than current activity. The FFS is a systemic prognostic tool. For skin-limited ICCV, no validated clinician-rated activity instrument existed prior to this study. The DLQI, cited in the original manuscript for context, is a patient-reported QoL measure, not an activity scale; QoL data were not prospectively collected in this study - acknowledged as a limitation. Both DLQI and patient-reported outcome measures will be incorporated as prespecified endpoints in the planned prospective multicenter validation study.

The strong inter-rater agreement ($\kappa_w = 0.85$) and the significant increases in treatment intensity and relapse across activity grades confirm that the scale captures clinically meaningful variance and is reproducible across two independent raters. The AUC of 0.72 for Grade III discrimination is in the acceptable-to-good range and suggests that the scale, while not perfect, provides substantially better than chance discrimination of high-activity disease - sufficient for its proposed clinical stratification function. External validation in an independent cohort is the immediate research priority.

Regarding power: no a priori calculation was performed in this exploratory descriptive study. Post-hoc power analysis confirms approximately 80% power to detect $OR \geq 2.0$ at $\alpha=0.05$. Individual comorbidity category associations are underpowered after Bonferroni correction and are characterized as hypothesis-generating. Key limitations include: cross-sectional design precluding causal inference; single-center design; selective biopsy (though sensitivity analysis is consistent with the primary result); absence of QoL data; and no external validation of the activity scale.

5. Conclusions

After multivariable adjustment for age, sex, disease duration, and nosological form, comorbidity burden (OR =

1.68 per additional condition; $p < 0.001$), metabolic/vascular comorbidity (OR = 2.14; $p=0.015$), and hepatic comorbidity (OR = 1.87; $p=0.048$) were independently associated with higher ICCV activity grade. The four-variant clinico-morphological classification and three-grade activity scale demonstrated strong inter-rater reliability ($\kappa_w = 0.85$) and significant predictive validity for treatment intensity and relapse. These are cross-sectional associations; causal inference requires longitudinal study.

From a clinical perspective, systematic comorbidity evaluation - with emphasis on metabolic-vascular risk factors and hepatitis B/C serological screening - should be integrated into the diagnostic pathway for all ICCV patients, as these conditions are independently associated with more severe and treatment-refractory disease. In HCV-endemic settings, cryoglobulin profiling should be considered in all LCV patients with Grade II–III activity or hepatic comorbidity.

Future priorities: (1) multicenter prospective validation of the activity scale with universal biopsy and DIF; (2) longitudinal follow-up to test whether comorbidity optimization reduces activity grade; (3) incorporation of DLQI and patient-reported outcomes; (4) cryoglobulin quantification in HCV-associated ICCV to mechanistically link cryoglobulin levels to disease severity grades.

Ethics Approval

SamSMU Ethics Committee No. 07/2023 (10 January 2023).

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