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Original Article

Characteristics of infusion-related reactions to lecanemab in early Alzheimer's disease: A multicenter real-world study in Northwestern China

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ABSTRACT

Background: Infusion-related reactions (IRRs) represent the most common adverse events associated with lecanemab. However, real-world data on IRR characteristics and risk factors in Asian populations, particularly Chinese, remain scarce.

Methods: In a multicenter prospective registry, 139 patients with early Alzheimer's disease (AD) receiving lecanemab were included. IRRs were physician-confirmed. Multivariable logistic regression identified independent predictors.

Results: The cumulative IRR incidence was 12.36 %, highest at the first infusion (17.3 %) and decreased significantly thereafter ($P < 0.001$). Fever (54.2 %) and dizziness (16.7 %) were the most common symptoms. 45.8 % of IRRs occurred 2–24 hours after infusion. All IRRs were mild (Grade 1) and self-limited. Hypertension (OR = 5.017, $P = 0.007$) and higher Fazekas score (OR = 2.734, $P = 0.017$) were independently associated with IRR.

Discussion: In this Chinese real-world cohort, lecanemab-associated IRRs were less frequent, mild, and delayed. Hypertension and white-matter hyperintensity severity emerged as key risk factors, underscoring the potential role of cerebrovascular health in IRR susceptibility.

1. Introduction

Alzheimer's disease (AD) is the most prevalent cause of cognitive impairment and dementia, accounting for approximately 60 %–70 % of all dementia cases [1]. The accumulation of amyloid-β (Aβ) in the brain is a well-established pathological hallmark and early event in AD pathogenesis [2]. Consequently, strategies aimed at clearing Aβ, including active and passive immunotherapies, have become a major focus in the development of disease-modifying therapies (DMTs) [3,4].

Lecanemab, a recombinant humanized IgG1 monoclonal antibody that selectively targets soluble Aβ protofibrils and insoluble fibrils, has emerged as the first globally approved anti-Aβ monoclonal antibody for the treatment of early AD (mild cognitive impairment or mild dementia due to AD) [5–7]. The phase 3 Clarity AD trial demonstrated that

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lecanemab effectively reduced cerebral Aβ burden and slowed the clinical progression of AD [8]. However, as lecanemab's clinical use expands, careful evaluation of its safety profile is essential.

Infusion-related reactions (IRRs) represent the most common adverse events associated with lecanemab administration [8–10]. In Clarity AD, IRRs occurred in 26.4 % of participants, predominantly during or within 30 minutes after infusion [10]. Reported symptoms included fever, influenza-like symptoms (chills, myalgia, arthralgia), nausea, vomiting, blood-pressure fluctuations, dyspnea, headache, sweating, chest discomfort, and skin irritation.

Notably, reported IRR rates appear to vary across populations. While real-world studies from Western settings describe an incidence of around 20 %, data from Asian cohorts suggest a lower frequency [11–13]. A regional Asian analysis of the Clarity AD trial reported an IRR incidence of approximately 12.3 %, and a recent multicenter study in Southern China observed rates between 5.88 % and 9.1 % [11,12]. This disparity underscores a critical gap in real-world evidence regarding the safety profile of lecanemab across different ethnic and geographic populations, particularly in Asia. Moreover, factors that may predispose patients to IRR remain poorly characterized, limiting the ability to implement tailored risk-mitigation strategies.

To address these evidence gaps, we conducted a multicenter, prospective, real-world registry study in Northwestern China (Lecanemab in Early AD, LEAD). This study aims to systematically characterize the clinical manifestations, timing, and independent risk factors of lecanemab-associated IRRs in a Northwest Chinese cohort, with the goal of informing safer clinical administration and optimized monitoring protocols.

2. Methods

2.1. Study design and participants

The LEAD study was a multicenter, prospective, real-world registry study conducted across 13 hospitals in Northwestern China. From July 2024 to September 2025, consecutive patients with early AD who were treated with lecanemab were enrolled.

The sample size was estimated based on a previously reported IRR incidence of 12.3 % in an Asian population[11], with α=0.05, power=80 %, and an assumed attrition rate of 10 %. This yielded a minimum target of 130 participants; the final sample comprised 139 patients.

The study protocol was approved by the Ethics Committee of the First Affiliated Hospital of Xi'an Jiaotong University (Approval No. XJTUIAF20241SYY-186–01). Written informed consent was obtained from all participants or their legally authorized representatives. The trial was prospectively registered with the Chinese Clinical Trial Registry (ChiCTR2400087134).

2.2. Treatment protocol

The treatment protocol followed the Chinese Expert Consensus on Disease-Modifying Therapy for Alzheimer's Disease [9]. All patients met the National Institute on Aging and the Alzheimer's Association (NIA-AA) criteria for early AD and had evidence of Aβ pathology confirmed by Aβ positron emission tomography (PET) or cerebrospinal fluid (CSF) tests indicative of AD. Lecanemab was administered intravenously at a dose of 10 mg/kg body weight, diluted in 250 mL of sterile saline, and infused over 1 hour using a low-protein-binding infusion set [14]. No routine premedication (e.g., acetaminophen, antihistamines, glucocorticoids) was administered before infusions. All infusions were performed in hospital settings. Vital signs, including heart rate, blood pressure, respiratory rate, and oxygen saturation, were continuously monitored during infusion, and all adverse events were documented. Following the first infusion, patients were observed as inpatients for 24 hours; after subsequent infusions, observation lasted 3 hours prior to discharge. In the event of suspected adverse reactions, patients or caregivers promptly notified the attending physician, who recorded the onset and resolution of symptoms, clinical manifestations, severity, and management using a standardized IRR checklist. Each suspected IRR was independently adjudicated by two neurologists, and any discrepancies were resolved through consensus to exclude amyloid-related imaging abnormalities (ARIA), infection, or drug interactions.

2.3. Data collection

Demographic characteristics (sex, age, education), clinical history (duration of symptoms), lifestyle factors (smoking, alcohol use), and comorbidities (hypertension, diabetes) were collected via medical records and structured interviews. Smoking was defined as consumption of ≥10 cigarettes per day for at least six months (current and former smokers were grouped together). Alcohol use was defined as the consumption of any alcoholic beverage at least once per week. Hypertension was defined as systolic/diastolic blood pressure ≥140/90 mmHg on three non-consecutive measurements during the hospitalization or current use of antihypertensive medication [15,16]. Diabetes was defined as hemoglobin A1c ≥6.5 %, fasting plasma glucose ≥7.0 mmol/L, or use of antidiabetic medication [17,18]. Laboratory tests (fasting glucose, estimated glomerular filtration rate, lipid profile) were performed centrally at the First Affiliated Hospital of Xi'an Jiaotong University. All participants underwent non-contrast brain magnetic resonance imaging (MRI), including T2-weighted fluid-attenuated inversion recovery (FLAIR), susceptibility-weighted imaging (SWI), diffusion-weighted imaging (DWI), and 3D T1-weighted sequences, preferably using a 3.0-T scanner, to confirm eligibility for lecanemab therapy.

White matter hyperintensity (WMH) burden was graded on T2-FLAIR sequences using the Fazekas scale (0–3) by two independent neuroradiologists, each with ≥5 years of experience in AD imaging. The scale is defined as: 0 = none or a single punctate WMH lesion; 1 = multiple punctate lesions; 2 = beginning confluence of lesions (bridging), and 3 = large confluent lesions [19,20].

Medial temporal lobe atrophy (MTA) score was independently assessed by two neuroradiologists as well, rated on 3D T1-weighted images, on the coronal slice parallel to the brainstem axis and passing through the aqueduct of Silvius. Both hemispheres were assessed, providing a 0–4 score according to the following criteria: 0 = no atrophy; 1 = widening of the choroid fissure; 2 = additional widening of the temporal horn of the lateral ventricle and slightly decreased hippocampal height; 3 = moderate loss of hippocampal volume; and 4 = end-stage increase of all these findings [21,22]. The highest score from the two hemispheres was recorded as the patient's score. For each scale, discrepancies between raters were resolved through joint review and consensus.

2.4. Definition and grading of IRR

IRR was defined as any new-onset symptom (e.g., fever, headache, rash, or myalgia/arthralgia) that emerged during or within hours after lecanemab infusion, after excluding other possible causes; delayed reactions beyond 72 hours were also included [23]. Each event was initially evaluated by the attending physician and subsequently confirmed by the two independent neurologists. To enhance diagnostic specificity, potential confounding conditions—including ARIA (assessed via MRI and clinical scales), infection (evaluated with inflammatory markers and microbiological testing when indicated), and drug interactions (reviewed through medication history and temporal analysis)—were systematically ruled out before final adjudication. The severity of IRRs was graded according to the Common Terminology Criteria for Adverse Events (CTCAE), version 5:

Grade 1. Mild, transient reaction; no intervention required.

Grade 2. Infusion interruption required; symptoms resolved with

symptomatic treatment.

Grade 3. Persistent or recurrent symptoms after initial improvement.

Grade 4. Life-threatening reaction requiring emergency intervention.

Grade 5. Death.

2.5. Statistical analysis

All data were entered into the YinFaTong electronic database. Statistical analyses were performed using SPSS version 26.0 (IBM Corp., Armonk, NY, USA). Continuous variables with normal or approximately normal distribution were expressed as mean ± standard deviation ($\overline{x} \pm s$), while non-normally distributed variables were expressed as median (interquartile range, IQR). Categorical variables were expressed as frequency and percentage [n (%)]. Group comparisons were performed using the *t*-test for normally distributed variables, the Mann–Whitney U test for nonparametric variables, and the χ^2 test for categorical variables.

Binary logistic regression was used for multivariate analysis to identify independent predictors of IRR (dependent variable: IRR = 1, non-IRR = 0). To control for potential confounding, the following covariates were included in the model: age, sex, uncontrolled hypertension, statin use, Fazekas score, and apolipoprotein E (APOE) ε4 carrier status. A two-step approach was employed: first, univariate screening was conducted with a threshold of $P < 0.10$, and then both statistically significant and clinically important variables were jointly entered into the final model. Multicollinearity was checked using the variance inflation factor (VIF), with values < 5 indicating acceptable collinearity. For verifying robustness, sensitivity analyses were performed, including excluding missing or extreme values and adjusting different combinations of covariates; the main conclusions remained consistent. Odds ratios (OR) with 95 % confidence intervals (CI) were computed, and a two-tailed $P < 0.05$ was considered statistically significant.

3. Results

3.1. Baseline characteristics

A total of 139 patients from 13 hospitals in Northwestern China received lecanemab therapy between July 2024 and September 2025. The cohort had a mean age of 67.6 ± 10.0 years (range 38–88); 61.9 % were female; and 51.8 % were carriers of at least one APOE ε4 allele. Based on diagnostic classification, 12.9 % had mild cognitive impairment due to AD and 87.1 % had mild AD dementia. Amyloid pathology was confirmed by Aβ-PET in 40.3 % of patients and by CSF biomarkers in 64.7 % (Table 1).

3.2. IRR incidence and trend

The 139 patients received a total of 712 lecanemab infusions. Among them, 107 completed ≥2 infusions, with the maximum number of infusions being 32. A total of 31 patients experienced at least one IRR during the entire treatment course. Overall, 88 IRR events were recorded, corresponding to a cumulative IRR incidence of 12.36 % (88/712). No patients discontinued treatment due to IRRs.

IRR events occurred in 24 patients (17.3 %) during the first infusion, 11 (10.3 %) during the second, 9 (9.1 %) during the third, 6 (6.2 %) during the fourth, 7 (7.4 %) during the fifth, 7 (8.0 %) during the sixth, and 3 (3.4 %) during the seventh infusion. No IRR events were recorded beyond the eighth infusion. A significant downward trend in IRR incidence was observed with increasing infusion number ($\chi^2 = 11.726$, $P < 0.001$), suggesting a potential adaptive or tolerance effect to repeated exposure (Fig. 1). A subset of patients experienced repeated IRRs. IRR

Table 1
Baseline characteristics of patients and comparisons between IRR and non-IRR groups.

Variables	Total (N=139)	IRR (N=31)	Non-IRR (N=108)	*P* value
Female—no. (%)	86 (61.9 %)	22(71.0 %)	64(59.3 %)	0.238
Age—year ($\overline{x}\pm s$)	67.6 ± 10.0	69.1 ±10.2	67.1±10.2	0.327
Years of education—*M* (Q_1, Q_2)	12.0 (9.0, 15.0)	13.0(9.5, 15.0)	12.0(9.0, 15.0)	0.581
Comorbidities—no. (%)				
Hypertension	24(17.3 %)	11(35.5 %)	13(12.0 %)	**0.002**
Diabetes	17(12.2 %)	6(19.4 %)	11(10.2 %)	0.171
Dyslipidemia	16(11.5 %)	6(19.4 %)	10(9.3 %)	0.197
Coronary heart disease	11(7.9 %)	2(6.5 %)	9(8.3 %)	1.000
Fazekas score ($\overline{x}\pm s$)	1.04 ±0.72	1.37 ±0.84	0.95±0.66	**0.016**
MTA score ($\overline{x}\pm s$)	1.73 ±0.77	1.59 ±0.73	1.78±0.78	0.267
Presence of baseline cerebral microbleeds—no. (%)	42(30.2 %)	11(35.5 %)	31(28.7 %)	0.564
Time since onset of symptoms—yr. ($\overline{x}\pm s$)	2.97 ± 1.94	3.03 ±1.52	2.96±2.06	0.853
Clinical subgroup—no. (%)				
Dementia due to AD	121 (87.1 %)	27(87.1 %)	94(87.0 %)	0.993
Mild cognitive impairment due to AD	18(12.9 %)	4(12.9 %)	14(13.0 %)	
Concomitant medications—no. (%)				
Cholinesterase inhibitors	93(66.9 %)	21(67.7 %)	72(66.7 %)	0.911
Neurotrophic agents	37(26.6 %)	10(32.3 %)	27(25.0 %)	0.420
Antihypertensive drugs	21(15.1 %)	8(25.8 %)	13(14.0 %)	0.059
Antidiabetic drugs	17(12.2 %)	5(16.1 %)	12(11.1 %)	0.454
Statins	38(27.3 %)	14(45.2 %)	24(22.2 %)	**0.012**
Aspirin	13(9.4 %)	4(12.9 %)	9(8.3 %)	0.443
MMSE ($\overline{x}\pm s$)	18.3 ± 6.1	19.69 ±4.80	17.66±6.63	0.278
CDR-SB, *M* (Q_1, Q_2)	4.5(3.0, 6.0)	4.8(3.9, 6.0)	4.5(3.0, 6.0)	0.464
ADAS-cog, *M* (Q_1, Q_2)	16.1 (11.7, 20.5)	15.9(12.0, 19.0)	16.3(11.0, 23.0)	0.561
ADCS-ADL, *M* (Q_1, Q_2)	64.0 (58.3, 67.0)	64.0(59.0, 67.0)	62.0(56.5, 67.5)	0.334
APOE ε4 status—no. (%)				
APOE ε4 noncarrier	67(48.2 %)	12(38.7 %)	55(50.9 %)	0.230
APOE ε4 carrier	72(51.8 %)	19(61.3 %)	53(49.1 %)	
Homozygotes	14(10.1 %)	6(19.4 %)	8(7.4 %)	
Heterozygotes	58(41.7 %)	13(41.9 %)	45(41.7 %)	
Diagnosed by—no. (%)				
Aβ-PET	56(40.3 %)	14(45.2 %)	42(38.9 %)	/
CSF biomarker	90(64.7 %)	19(61.3 %)	71(65.7 %)	
Aβ-PET & CSF biomarker	7(5.0 %)	2(6.5 %)	5(4.6 %)	

Abbreviations: AD, Alzheimer's disease; MTA, Medial temporal lobe atrophy score; MMSE, Mini-Mental State Examination; CDR-SB, Clinical Dementia Rating-Sum of Boxes; ADAS-cog, cognitive subscale of the Alzheimer's Disease Assessment Scale; ADCS-ADL, Alzheimer's Disease Cooperative Study–Activities of Daily Living Scale; APOE, apolipoprotein E; Aβ-PET, amyloid-β positron emission tomography; CSF, cerebrospinal fluid.

symptoms in this subgroup tended to lessen with increasing numbers of infusions. For example, regarding fever, both the peak body temperature and the duration of fever decreased progressively with subsequent infusions (Table S1).

3.3. Clinical manifestations of IRR

During the first infusion, 24 patients experienced IRR, accounting for 29 individual IRR symptoms documented. The most common manifestation was fever, occurring in 54.2 % (13/24) of patients, followed by dizziness in 16.7 % (4/24), headache or head pressure in 8.3 % (2/24), generalized myalgia in 8.3 % (2/24), and rash in 8.3 % (2/24). Less frequent reactions included arthralgia and swelling, tachycardia, pruritus, throat discomfort, hypotension, and fatigue, each reported by one patient (4.2 %, 1/24). 3 patients reported two concurrent symptoms (Fig. 2).

3.4. Timing of IRR events during the first infusion

Among 24 first-infusion IRR events, only 20.8 % (5/24) occurred during the infusion itself. The majority (45.8 %, 11/24) manifested in the 2–24 hours window post-infusion, 20.8 % (5/24) at 24–48 hours, 8.3 % (2/24) at 48–72 hours and 4.2 % (1/24) beyond 72 hours after infusion (Fig. 3). The earliest observed IRR was throat discomfort, which arose 30 min after infusion initiation. The latest event was scattered rash on the limbs, reported by the caregiver on day 7 after infusion. (Fig. 3).

Fever predominantly occurred within 24 hours (92.3 %, 12/13), particularly within the first 12 hours post-infusion (76.9 %, 10/13). Symptoms such as dizziness, headache, and head pressure most commonly appeared on days 1–2 after infusion (50.0 %, 3/6).

3.5. Duration and outcomes of IRR

All IRR events were classified as Grade 1 (mild) according to CTCAE criteria. No anaphylaxis was observed. Fever and chills resolved within 4 days after infusion in all affected patients. Symptoms of dizziness, headache, or head pressure resolved within one week in 87 % of affected

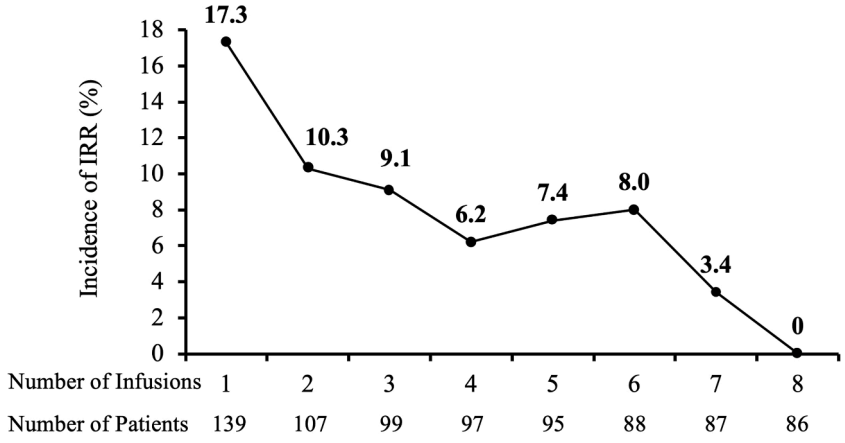

Fig. 1. Incidence of IRR by infusion number. The incidence of IRR was highest following the first lecanemab infusion (17.3 %) and declined significantly with subsequent administrations ($\chi^2 = 11.726$, $P < 0.001$). No IRR events were recorded beyond the eighth infusion. IRR, infusion-related reaction.

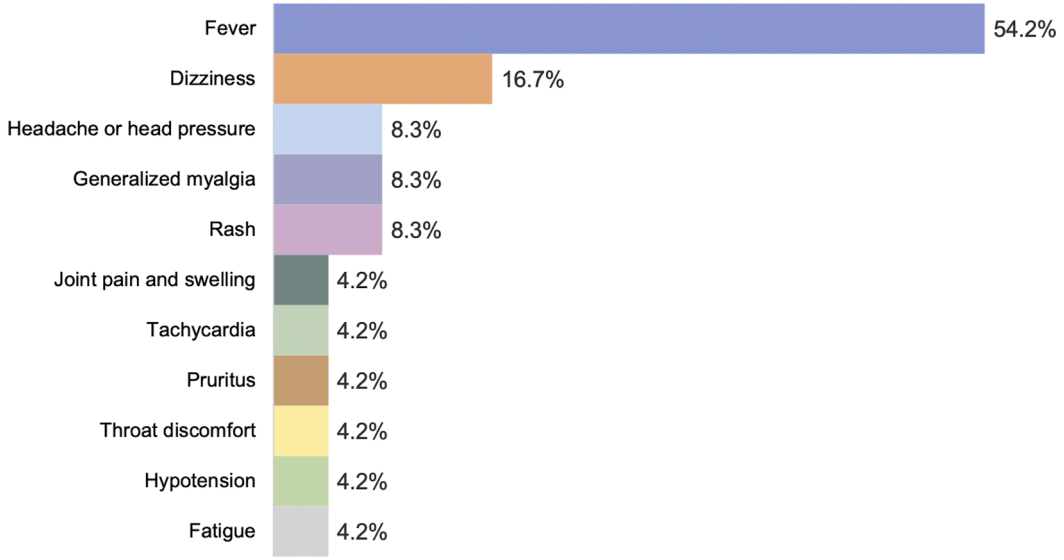

Fig. 2. Clinical manifestations of IRR during the first lecanemab infusion (n = 24 patients). Data represent the proportion of patients experiencing each symptom. Fever was the most common presentation (54.2 %). Some patients reported more than one symptom. IRR, infusion-related reaction.

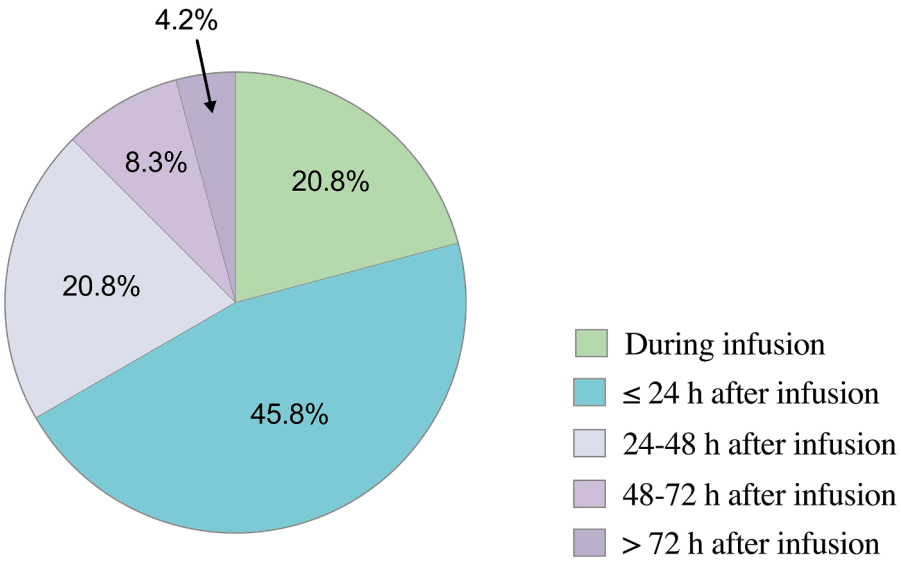

Fig. 3. Timing of IRR onset relative to the first lecanemab infusion. The majority of IRRs (45.8 %) occurred in the 2–24 hours window post-infusion. Only 20.8 % of events were observed during the infusion itself. IRR, infusion-related reaction.

patients and required no specific intervention. Transient tachycardia or bradycardia did not compromise hemodynamic stability and resolved spontaneously within 3 hours post-infusion. Myalgia/arthralgia subsided within 14 hours post-infusion, and rashes resolved spontaneously within one week. Two patients with pruritus received loratadine for symptomatic relief.

IRR events were managed with symptomatic treatment [loratadine for pruritus and physical cooling measures or nonsteroidal antipyretic analgesics (e.g., acetaminophen) were administered based on the preferences of the patients and their caregivers for fever and chills] Caregivers were trained to recognize delayed symptoms (e.g., fever 2–24 hours post-infusion) .This is a critical step for AD patients with cognitive impairment who may not report symptoms independently [24].

No patients required interruption of infusion due to IRRs.

3.6. Factors associated with IRR occurrence

All patients were divided into two groups according to the presence or absence of IRR events during the entire treatment period. Univariate analysis showed that patients in the IRR group had a significantly higher prevalence of hypertension (35.5 % vs. 12.0 %, $P = 0.002$), higher mean Fazekas scores (1.37 ± 0.84 vs. 0.95 ± 0.66, $P = 0.016$), and more frequent statins use (45.2 % vs. 22.2 %, $P = 0.012$) compared with those in the non-IRR group (Table 1). No significant differences were observed between the two groups in sex, age, APOE ε4 carrier status, MTA score, MMSE score, CDR-SB score, or other comorbidities and concomitant medications (Table 1).

3.7. Multivariate analysis of risk factors for IRR

To identify risk factors for IRR, a binary logistic regression analysis was performed with the presence of IRR (no = 0, yes = 1) as the dependent variable. Independent variables included age, sex (male = 0, female = 1), hypertension (no = 0, yes = 1), diabetes (no = 0, yes = 1), statin use (no = 0, yes = 1), aspirin use (no = 0, yes = 1), Fazekas score, and APOE ε4 carrier status (non-carrier = 0, carrier = 1).

The results identified hypertension (OR = 5.017, 95 % CI: 1.547–16.268, $P = 0.007$) and a higher Fazekas score (OR = 2.734, 95 % CI: 1.198–6.239, $P = 0.017$) as independent predictors of IRR. Female sex (OR = 3.101, 95 % CI: 0.974–9.870, $P = 0.055$) and statin use (OR = 2.955, 95 % CI: 0.966–9.040, $P = 0.058$) showed associations with IRR risk that approached, but did not reach statistical significance (Table 2). No significant collinearity was detected among model variables (all VIF < 2).

4. Discussion

Consistent with the phase 3 Clarity AD trials, our study confirms that IRRs are the most common adverse events associated with lecanemab administration. To our knowledge, this is the first multicenter, real-world registry to systematically characterize the clinical profile, timing, and risk factors of lecanemab-associated IRRs in the Chinese population, yielding three principal findings.

4.1. Lower incidence, mild severity, and delayed onset characterize IRRs in this cohort

The cumulative IRR incidence of 12.36 % in our cohort is lower than the 26.4 % reported in the Clarity AD trial and aligns more closely with rates observed in other Asian studies (5.88 %–12.3 %) [10–13]. Consistent with previous reports, most IRR events in our study were mild (CTCAE Grade 1), presenting mainly as mild fever that resolved within 3–4 days without intervention [25].

In contrast to global trial data, where the majority of IRRs occur during or within 30 min after infusion (only 30 % delayed IRRs) [8], our real-world data demonstrate a pronounced delay: 79.2 % of events occurred ≥1 hour post-infusion, with a clear peak (45.8 %) in the 2–24 hour window. This delay likely stems from two factors: first, cognitive impairment may cause patients to overlook mild symptoms such as

Table 2
Multivariate logistic regression analysis of risk factors for IRR.

Variables	β	S.E.	Wald χ^2	P value	OR (95 % *CI*)
Sex	1.132	0.591	3.671	**0.055**	3.101 (0.974~9.870)
Age	-0.051	0.032	2.567	0.109	0.950 (0.892~1.012)
Hypertension	1.613	0.600	7.221	**0.007**	5.017 (1.547~16.268)
Diabetes	0.570	0.709	0.646	0.422	1.769 (0.440~7.104)
Statins use	1.083	0.571	3.605	**0.058**	2.955 (0.966~9.040)
Aspirin use	-1.155	0.948	1.486	0.223	0.315 (0.049~2.018)
Fazekas score	1.006	0.421	5.712	**0.017**	2.734 (1.198~6.239)
APOE ε4 status	0.828	0.553	2.243	0.134	2.288 (0.774~6.762)

Abbreviations: IRR, infusion-related reaction; OR, odds ratios; APOE, apolipoprotein E.

myalgia until they are identified at the 24-hour follow-up; second, blood-brain barrier (BBB) dysfunction in individuals with cerebral small vessel disease can prolong the release of inflammatory mediators [25]. Collectively, these observations indicate Asian populations may have a lower risk of IRRs in lecanemab treatment. It also suggests that for patients receiving lecanemab, the post-infusion monitoring window should be extended to at least 24 hours, and home monitoring education for patients and caregivers should be reinforced to avoid delayed recognition or mismanagement of late-onset IRRs.

Moreover, existing IRR studies lack a detailed characterization of "delayed IRRs" (occurring >1-hour post-infusion). Global trials focus on intra-infusion or 30-minute post-infusion monitoring [8], but regional Asian analysis hints at delayed onset: 38.7 % of IRRs occurred >1-hour post-infusion [11], raising concerns about under detection with standard monitoring. For patients in Northwestern China—who often have more limited access to healthcare and carry a higher burden of vascular comorbidity—clarifying the timing and risk factors of IRRs is essential to optimize treatment safety.

4.2. IRR occurs predominantly in the first infusion and declines with subsequent infusions

Consistent with previous reports, IRRs occurred predominantly during the first infusion and declined with subsequent administrations. In the present study, the incidence of IRR in the first infusion was 17.3 %, decreasing thereafter, with no IRR observed after the eighth infusion. This pattern aligns with the immunogenic characteristics of lecanemab and the potential development of rapid immune tolerance [26], suggesting that repeated exposure to monoclonal antibodies may reduce IRR risk as the immune system adapts.

4.3. Hypertension and a higher Fazekas score are key risk factors

Currently, no available data clearly delineate the risk factors associated with IRRs to lecanemab. Our study identifies that hypertension and a higher Fazekas score were significantly associated with an increased risk of IRR. While the precise mechanisms are not yet fully elucidated, we hypothesize that these factors likely serve as proxies for underlying cerebrovascular vulnerability. The coexistence of hypertension and advanced white matter lesions reflects a more vulnerable BBB and chronic cerebrovascular injury. Lecanemab, as an anti-Aβ monoclonal antibody, may activate immune cells, leading to the release of inflammatory mediators [27–29]. These mediators may more easily diffuse into perivascular or systemic spaces in patients with BBB fragility, amplifying peripheral inflammatory responses and manifesting as symptoms like fever and dizziness. Furthermore, we speculate that lecanemab-induced immune activation may disproportionately affect individuals with a pre-existing fragile neurovascular unit, thereby enhancing systemic inflammatory responses and increasing the likelihood of IRR.

Notably, female sex and statin use showed trends toward increased IRR risk, but did not reach statistical significance. Given the limited sample size and wide confidence intervals, these findings should be interpreted cautiously. Further studies with larger sample sizes are needed to clarify whether these associations are reproducible.

4.4. Limitation

This study has several limitations. First, the sample size was relatively small, and the follow-up duration was limited. Although conducted across 13 centers, the number of patients experiencing IRR was relatively small (n=31), and the number of hypertensive individuals was limited, which may constrain statistical precision. To mitigate this, we restricted covariate entry based on clinical relevance and univariate screening thresholds, and conducted sensitivity analyses that yielded consistent results. Nevertheless, the confidence intervals for some predictors were relatively wide, and the findings should be interpreted as hypothesis-generating. Larger multicenter studies with external validation are warranted to confirm these associations.

Second, IRR identification relied on physician judgment and patient/caregiver reporting, which may have led to under-reporting of mild or delayed events. We suggest that future studies implement standardized, prospective patient-reported outcome questionnaires to capture all events systematically.

Third, unmeasured or inadequately quantified factors—such as individual immune status, nuances in concomitant medications, or genetic background—might still influence IRR risk. These require further exploration in larger, well-stratified cohorts to refine the risk prediction model.

Fourth, there are potential limitations regarding the Fazekas scoring. Although imaging analysis was centralized, readers were not blinded to clinical data. Furthermore, the heterogeneity in MRI scanner protocols and raters' experience may have introduced systematic variability in the classification of white-matter lesions at baseline, which could introduce bias into the Fazekas scoring.

4.5. ConclusionIn summary, this multicenter, real-world registry found that in Northwestern China, the incidence of IRR during lecanemab therapy for early AD was lower. Notably, the majority of IRRs occurred 2–24 hours post-infusion, rather than during the infusion itself. Patients with hypertension or higher Fazekas scores had an increased risk of IRRs, while females and statin users showed a trend toward increased IRR risk. These results may assist clinicians in identifying high-risk patients, guide individualized risk management strategies, and offer new insights into the pathophysiological mechanisms of IRRs. Furthermore, the association with cerebrovascular health markers offers novel clues regarding the pathophysiology of these reactions, suggesting a potential interplay between anti-amyloid immunity and vascular integrity. However, further large-scale, prospective studies are warranted to validate these risk predictors and to elucidate the underlying biological mechanisms. Additionally, the current practices for IRR prevention, management, and reporting lack cross-institutional standardization, indicating gaps in quality and safety oversight. We recommend the adoption of a standardized protocol that includes comprehensive pre-infusion risk assessment, vigilant intra-infusion monitoring, and stratified post-infusion management. This protocol should involve extended monitoring (≥30 min) for at least the first infusion and the precise use of premedication (e.g., antihistamines, glucocorticoids) in identified high-risk populations.

List of abbreviations

AD	Alzheimer's disease
Aβ	Amyloid-β
APOE	Apolipoprotein E
ARIA	Amyloid-related imaging abnormalities
BBB	Blood-brain barrier
CI	Confidence intervals
CSF	Cerebrospinal fluid
CTCAE	Common Terminology Criteria for Adverse Events
DMT	Disease-modifying therapies
DWI	Diffusion-weighted imaging
FLAIR	Fluid-attenuated inversion recovery
IQR	Interquartile range
IRRs	Infusion-related reactions
LEADS	Lecanemab in Early AD
MTA	Medial temporal lobe atrophy
MRI	Magnetic resonance imaging
NIA-AA	National Institute on Aging and the Alzheimer's Association
OR	Odds ratios
PET	Positron emission tomography
SWI	Susceptibility-weighted imaging
VIF	Variance inflation factor
WMH	White matter hyperintensity

Declarations

Consent statement

Written informed consent was obtained from all participants or their legally authorized representatives. This study was conducted in accordance with the Declaration of Helsinki and the study protocol was approved by the Ethics Committee of the First Affiliated Hospital of Xi'an Jiaotong University (Approval No. XJTUIAF20241SYY-186–01).

Trial registration

ChiCTR2400087134 [Registration Date: 2024–07–22].

Ethics approval

XJTUIAF20241SYY-186–01 [Ethics Approval Date: 2024–07–03].

Data availability statement

Research data are not shared due to ethical restrictions.

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Declaration of the use of generative AI and AI-assisted technologies in scientific writing and in figures, images and artwork

During the preparation of this work, the authors used ChatGPT to improve language. After using it, the authors reviewed and confirmed the content as needed and take full responsibility for the content of the publication.

CRediT authorship contribution statement

Peijie Liu: Writing – original draft, Formal analysis, Data curation. **Jie Liu:** Writing – original draft, Formal analysis, Data curation. **Jin Wang:** Data curation. **Ying Du:** Data curation. **Zhirong Liu:** Data curation. **Hong Zhang:** Data curation. **Aiqin Zhu:** Data curation. **Gejuan Zhang:** Data curation. **Xinling Meng:** Data curation. **Chunmei Zhao:** Data curation. **Weiping Zhang:** Data curation. **Liangjun Dang:** Data curation. **Wei Zhang:** Writing – review & editing, Conceptualization. **Qiumin Qu:** Writing – review & editing, Conceptualization. **Yan Qu:** Writing – review & editing, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.tjpad.2026.100542.

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