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Clinical Characteristics and Risk Factors of Hypersensitivity Reactions to Iron Isomaltoside in Gynaecological Patients with Iron Deficiency Anaemia: A Retrospective Pharmacovigilance Study

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Abstract

Background Intravenous iron isomaltoside is a third-generation iron replacement widely used for perioperative gynaecological iron deficiency anaemia (IDA). Multiple international reports have documented hypersensitivity reactions (HSRs) following infusion, yet large-scale real-world data focusing on Chinese gynaecological cohorts remain absent. This study aimed to characterise the clinical phenotypes and identify independent risk predictors of iron isomaltoside-associated HSRs to guide safer clinical administration.

Methods A single-centre retrospective nested case–control pharmacovigilance analysis was performed using data extracted from the China Hospital Pharmacovigilance System (CHPS). All gynaecological inpatients receiving iron isomaltoside between July 2024 and December 2025 were screened. Confirmed HSRs were defined as cases with Naranjo causality score ≥ 5; each HSR case was 1:4 matched to control patients by primary gynaecological diagnosis, age (±5 years), and BMI (≤3 kg/m²). Multivariate logistic regression was applied to screen independent risk factors.

Results A total of 611 patients with 627 iron isomaltoside infusion episodes were enrolled, with 27 confirmed HSR cases identified (overall incidence 4.42%; CHPS alert positive rate 13.99%). All hypersensitivity events occurred during infusion, with a mean onset time of 25.33 ± 30.92 min, and 74.07% arose within the first 30 min. Cutaneous/mucosal and respiratory manifestations predominated, and all patients achieved full resolution after symptomatic intervention. Multivariate regression revealed three independent risk factors: concomitant intravenous antibiotic use (OR=4.38, 95%CI 1.44–13.36), elevated baseline platelet count (OR=1.01, 95%CI 1.01–1.01), and reduced pre-infusion haemoglobin concentration (OR=0.94, 95%CI 0.91–0.98).

Conclusions Iron isomaltoside-related HSRs predominantly develop within the initial 30 min of infusion in gynaecological IDA patients. Clinicians should implement intensified real-time monitoring for individuals receiving concurrent antibiotics, low baseline haemoglobin, or reactive thrombocytosis to minimise hypersensitivity risk. The CHPS platform enables efficient, large-scale real-time post-marketing drug safety surveillance for intravenous iron agents.

Background

Early generations of intravenous iron formulations carried substantial adverse reaction risks due to unstable carbohydrate-iron chelate structures. Iron isomaltoside injection, developed by Pharmacosmos (Denmark), represents a third-generation preparation with a tightly bound isomaltoside pentamer matrix that minimises labile iron release, permitting single high-dose rapid infusion without split administration[1]. It has become a standard therapeutic option for correcting perioperative anaemia in gynaecological tumour and uterine bleeding disorders, with well-established short-term efficacy[2].

Despite favourable pre-registration safety profiles, global post-marketing surveillance and case series have repeatedly reported mild-to-moderate hypersensitivity events linked to iron isomaltoside infusion[3, 4]. Regulatory authorities in Denmark and Spain have even issued restrictive clinical guidance owing to accumulating HSR safety signals[5, 6]. Iron isomaltoside was officially approved for clinical use in China in 2021; however, domestic published research largely focuses on therapeutic efficacy, lacking systematic real-world safety data specifically in Chinese gynaecological populations. No prior large-sample retrospective studies have quantified HSR incidence,

characterised clinical symptom profiles, or validated modifiable and laboratory-based risk factors within this patient subgroup.

This retrospective pharmacovigilance study leverages automated signal capture via the CHPS platform to fill this evidence gap. The primary objectives were to calculate the overall incidence of iron isomaltoside HSRs in hospitalised gynaecological IDA patients, describe the temporal and clinical features of hypersensitivity episodes, and identify independent baseline and medication-related risk factors for risk stratification and clinical risk reduction.

Methods

Study setting and data source

This retrospective active pharmacovigilance cohort and nested case–control study was conducted at the First Affiliated Hospital of Xiamen University, a tertiary teaching hospital designated as a national hospital adverse drug reaction (ADR) monitoring centre. All gynaecological inpatients administered iron isomaltoside injection (5 mL:500 mg, Pharmacosmos A/S, Denmark, administered via intravenous infusion) from 1 July 2024 to 15 December 2025 were screened via the CHPS integrated hospital information system text-mining module[7].

All automated safety alerts generated by CHPS underwent dual independent manual review by two qualified clinical pharmacists. Causal association between iron isomaltoside and suspected adverse events was assessed using the validated Naranjo ADR probability algorithm[8] and the Common Terminology Criteria for Adverse Events Version 5.0 (CTCAE v5.0). Disagreements in causality grading were resolved via group consensus discussion; patients with Naranjo score ≥ 5 were classified as confirmed HSR cases. Descriptive statistics summarised HSR onset latency, symptom remission duration, vital sign disturbances, clinical manifestations, and all supportive interventions administered.

Eligibility criteria

Inclusion criteria:

 Inpatients admitted to the gynaecology ward during the study window;

Clinically confirmed iron deficiency anaemia per national multidisciplinary diagnostic consensus, receiving ≥1 single iron isomaltoside infusion;

 No baseline inherited or acquired coagulation disorders.

Exclusion criteria

 Incomplete pre-infusion routine laboratory testing records;

 Decompensated chronic liver dysfunction;

 Non-iron deficiency anaemia aetiology (e.g., haemolytic anaemia);

 Iron overload or hereditary iron utilisation disorders (haemochromatosis);

 Pregnant individuals

Nested case–control matching design

To mitigate confounding bias from demographic and diagnostic variables, a 1:4 matched nested case–control framework was applied. Case patients presented confirmed iron isomaltoside HSRs; matched controls received identical iron isomaltoside treatment without any hypersensitivity manifestations. Matching criteria included identical primary gynaecological diagnosis (uterine leiomyoma, adenomyosis, ovarian cyst, uterine malignant neoplasm), age difference ≤ 5 years, and BMI difference ≤ 3 kg/m².

CHPS automated monitoring configuration

Signal capture rules were constructed following national ADR terminology guidelines[9], with automatic alerts triggered when all three below conditions were satisfied simultaneously:

 Valid electronic medication order for iron isomaltoside injection

 Patient discharge date falling within the defined study period

 Electronic medical record containing predefined hypersensitivity keywords linked by Boolean OR across organ systems:

•Respiratory: chest tightness, dyspnoea, wheeze, cough, sneezing

•Cutaneous/mucosal: pruritus, flushing, maculopapular rash

•Gastrointestinal: abdominal distension, abdominal pain, nausea, vomiting

•Neurological: headache, dizziness, back pain, paraesthesia

•Cardiovascular: tachycardia, palpitations, hypertension, hypotension

•Systemic: rigors, generalised diaphoresis

Collected observational variables:

 Demographic metrics: age, body mass index (BMI);

 Clinical historical variables: chronic comorbidities (hypertension, type 2 diabetes, asthma, chronic hepatitis B), documented drug allergy history, prior blood transfusion history, total duration of primary gynaecological disease;

 Infusion-related parameters: total iron isomaltoside administered dose, time interval between infusion and scheduled surgery, lag time from drug compounding to infusion initiation;

 Concomitant perioperative medications: oxytocin infusion, intravenous antibiotics administered within 24 h pre-infusion;

 Pre-infusion laboratory biomarkers and ECG findings: white blood cell count, red blood cell count, lymphocyte count, neutrophil count, platelet count (PLT), haemoglobin (HGB), alanine aminotransferase (ALT), aspartate aminotransferase (AST), total/direct/indirect bilirubin, serum creatinine, creatine kinase.

Statistical analysis

All statistical calculations were completed using SPSS 22.0 and Microsoft Excel 2021. Normality of continuous variables was verified via Shapiro–Wilk and Lilliefors tests. Normally distributed continuous data were presented as mean ± standard deviation (SD), compared via independent samples t-test; non-normal continuous data were summarised as median (interquartile range) [M (Q1, Q3)] and analysed with the Mann–Whitney U test. Categorical variables were reported as number (percentage) and intergroup differences evaluated using χ^2 tests.

All variables with univariate $P < 0.05$ were entered into a multivariate binary logistic regression model with HSR occurrence as the binary dependent outcome to identify independent risk factors. Two-tailed $P < 0.05$ was defined as the threshold for statistical significance.

Results

Overall cohort baseline characteristics

A total of 611 eligible gynaecological inpatients received 627 discrete iron isomaltoside infusions throughout the study period. The CHPS monitoring module generated 193 preliminary safety alerts, of which 27 episodes were validated as confirmed HSRs after manual causality assessment, yielding an overall HSR incidence of 4.42% (27/611) and an alert positive predictive value of 13.99%.

After 1:4 matching, the analytical dataset contained 27 HSR cases and 108 matched control participants. The case group had a mean age of 44.48 ± 7.60 years (range 31–67 years). Overlapping primary gynaecological diagnoses included uterine leiomyoma (18, 66.67%), adenomyosis (17, 62.96%), uterine malignancy (5, 18.52%), and ovarian cysts (3, 11.11%). Fifty-five point five six percent of patients reported primary disease duration < 6 months, with a maximum recorded disease duration of 13 years. Comorbidities included hypertension (3 patients), type 2 diabetes (2), chronic hepatitis B (2), and asthma (1). Eighty-eight point eight nine percent (24/27) underwent elective or emergency gynaecological surgery during hospitalisation.

Clinical manifestations and timeline of HSRs

Twenty-five of 27 case patients received the full 1000 mg iron isomaltoside dose, with only 2 patients administered the 500 mg reduced dose. Every hypersensitivity episode occurred during active intravenous infusion, with onset latency ranging from 1 min to 124 min, mean 25.33 ± 30.92 min; 74.07% of reactions emerged within the initial 30 min of infusion. Eighty-one point four eight percent of patients achieved complete symptom resolution within 60 min of intervention, with a mean remission time of 38.85 ± 41.13 min.

Recorded vital sign disturbances comprised tachycardia (4 patients), tachypnoea (8), elevated systemic blood pressure (10), and isolated hypotension (1). In total, 64 distinct hypersensitivity symptoms were documented, dominated by cutaneous/mucosal events (22 episodes, 34.37%) and respiratory complaints (17 episodes, 26.56%). The most prevalent individual clinical manifestations were facial flushing (8, 12.50%), chest tightness (8, 12.50%), dyspnoea (6, 9.38%), and generalised pruritus (6, 9.38%).

Infusion was permanently discontinued in 11 patients (40.74%) due to severe hypersensitivity symptoms; one patient experienced recurrent chest tightness after attempted infusion restart. The remaining 16 patients completed full iron replacement therapy after supportive interventions including temporary infusion pause, tubing

replacement, supplemental oxygen, continuous ECG monitoring, and intravenous dexamethasone administration combined with reduced infusion flow rate. Full individual patient-level HSR clinical data are summarised in Table 1.

Univariate intergroup comparisons

No statistically significant differences between case and control groups were detected for matching variables (primary diagnosis, age, BMI, all P > 0.05). Univariate statistical testing identified significant intergroup disparities for chronic comorbidity history, primary disease duration, concurrent intravenous antibiotic administration, abnormal pre-infusion ECG, baseline PLT count, pre-infusion HGB concentration, and baseline ALT level (all $P < 0.05$). No significant differences were observed for drug allergy history, prior blood transfusion, concomitant oxytocin use, total iron isomaltoside dose, infusion-surgery interval, compound-to-infusion lag time, or the majority of remaining laboratory biomarkers (all $P > 0.05$). Full univariate comparative data are presented in Table 2.

Multivariate logistic regression independent risk factors

All variables demonstrating $P < 0.05$ in univariate testing were incorporated into the multivariate logistic regression model. Three variables emerged as statistically significant independent risk factors for iron isomaltoside HSRs (all $P < 0.05$): Perioperative concurrent intravenous antibiotic use (OR=4.38, 95%CI: 1.44–13.36); Elevated pre-infusion platelet count (OR=1.01, 95%CI:1.01–1.01); Reduced baseline haemoglobin concentration (OR=0.94, 95%CI: 0.91–0.98). Complete regression coefficients, standard errors, Wald statistics, P-values, and odds ratio estimates with confidence intervals are provided in Table 3.

Discussion

Our institution has operated the CHPS automated pharmacovigilance platform since 2018 as a national ADR monitoring demonstration unit. Supported by national comprehensive clinical medication evaluation initiatives, our research team has constructed more than ten specialised automated safety monitoring modules within the CHPS framework, with validated applications for post-marketing re-evaluation and real-time irrational prescription warning[10–12]. In the present study, the HSR signal module delivered near-instant automated alert generation, with full manual causality adjudication completed within 24 h per alert, confirming the platform's high efficiency and timeliness for large-scale real-world intravenous iron safety surveillance.

Published international real-world studies report highly variable iron isomaltoside HSR incidence rates: UK primary care surveillance documented an incidence of only 0.4%[3], a Dutch single-centre cohort reported 8.7%[13], and a Pakistani retrospective hospital study recorded 7.29%[14]. Our observed incidence of 4.42% falls within this intermediate range yet substantially exceeds the 0.1–1% risk range stated within the domestic Chinese product labelling. This discrepancy likely arises from systematic under-recording of mild cutaneous hypersensitivity events in routine passive hospital reporting systems, indicating that product labelling should be updated to incorporate contemporary Chinese real-world pharmacovigilance evidence.

All commercial intravenous iron nanoparticle formulations carry inherent pseudoallergic reaction risk[15]. Consistent with prior international cohorts, 74.07% of our HSR cases developed symptoms within the initial 30 min of infusion, matching the 67.5% proportion reported by Mulder et al[13]. The predominant symptom spectrum (facial flushing, substernal chest tightness) aligns with the large multicentre FERWON-IDA randomised trial conducted by Auerbach et al[16]. Notably, rigors and severe shivering were entirely absent within our patient cohort,

representing a clear phenotypic distinction from IgE-mediated hypersensitivity to platinum and taxane chemotherapeutic agents[17].

We hypothesise this divergent clinical phenotype arises from distinct immunological mechanisms: chemotherapy-associated infusion reactions are typically true IgE-dependent allergies, while intravenous iron HSRs are consistent with complement activation-related pseudoallergy (CARPA)[18]. Nanoscale iron core particles activate circulating complement cascades, with product-specific reaction severity determined by core particle diameter, surrounding carbohydrate polymer architecture, and molecular packing density[19]. Further translational in vitro and animal mechanistic research is required to validate this pathway difference.

All 27 patients achieved complete symptom resolution with standard supportive hospital interventions. Rash and pruritus required longer recovery periods in several individuals, while 11 patients required permanent infusion cessation. Two participants presented classic Fishbane syndrome, an iron-specific non-life-threatening reaction defined by generalised flushing, dorsal back pain, chest tightness, and dyspnoea[20, 21]. This syndrome typically resolves rapidly after temporary infusion suspension without antihistamine or adrenaline rescue, and infusion may be safely resumed after full symptom abatement.

The remaining 16 patients completed full iron replacement after flow rate reduction, supplemental oxygen, and prophylactic intravenous dexamethasone. Rapid high initial infusion rates are a well-established modifiable HSR risk factor; international consensus guidance mandates a minimum total infusion duration of 60 min with ultra-slow initial delivery over the first 5–15 min[21]. Routine premedication with oral antihistamines is not recommended for patients receiving intravenous iron monotherapy, consistent with our institutional standard clinical practice[22].

Previous international studies have proposed advanced age, female sex, and chronic gastrointestinal disease as potential HSR modifiers[18]; however, these associations are heavily distorted by selection and reporting bias, as most published cohorts focus on gastroenterology anaemia populations, and females inherently bear higher iron deficiency prevalence. Our matched case–control design eliminated confounding from sex, primary diagnosis, age, and BMI to reduce this bias. We additionally evaluated compound-to-infusion lag time as a novel exploratory variable testing drug stability effects on hypersensitivity risk, though no significant association was identified. Similarly, total administered iron dose demonstrated no predictive value for HSR occurrence, consistent with prior retrospective cohort findings[23].

Concurrent perioperative intravenous antibiotic exposure emerged as the strongest independent modifiable risk factor (OR = 4.38). Cephalosporins constituted the primary perioperative prophylactic antibiotic within our gynaecological cohort, a drug class with intrinsic allergenic potential that amplifies complement activation when co-administered with nanoparticle iron formulations[24]. Clinicians should minimise overlapping iron isomaltoside and unnecessary intravenous antibiotic exposure where clinically feasible to reduce combined hypersensitivity risk.

Lower pre-infusion haemoglobin independently elevated HSR risk (OR = 0.94): each 1 g/L HGB reduction corresponded to a 6% increase in hypersensitivity odds. Conversely, each 1×10^9/L elevation in baseline platelet count increased risk by 1%. Most study patients carried adenomyosis, a condition causing chronic cyclic uterine blood loss, persistent tissue hypoxia, and sustained low-grade systemic inflammation that drives reactive thrombocytosis as a surrogate marker of disease severity and immune hyperresponsiveness[25]. Pre-infusion

complete blood count (HGB and PLT) therefore provides simple, readily available clinical biomarkers for rapid HSR risk stratification prior to iron infusion.

Study limitations

This research is restricted to a single tertiary hospital and exclusively gynaecological hospitalised female patients, limiting generalisability to male cohorts, outpatient populations, and non-gynaecological anaemia aetiologies. Granular electronic medical record data on exact infusion flow rates were unavailable and could not be incorporated into regression modelling. Despite these constraints, rigorous 1:4 matching substantially attenuated selection and diagnostic confounding.

Conclusions

This CHPS-based retrospective nested case–control pharmacovigilance study provides large-scale real-world safety evidence for iron isomaltoside infusion in Chinese gynaecological patients with iron deficiency anaemia. The overall HSR incidence was 4.42%, with most hypersensitivity events developing within the initial 30 min of infusion and predominantly presenting with cutaneous and respiratory symptoms. Concurrent intravenous antibiotic administration, low pre-infusion haemoglobin concentration, and elevated baseline platelet count were confirmed as independent risk factors for iron isomaltoside HSRs.

The CHPS automated signal surveillance system delivers rapid, scalable real-time post-marketing drug safety monitoring and fills an existing evidence gap regarding iron isomaltoside safety profiles within Chinese gynaecological populations. Routine clinical workflow should integrate pre-infusion evaluation of antibiotic necessity and baseline full blood count biomarkers, alongside intensified early-infusion vital sign monitoring for high-risk subgroups to reduce hypersensitivity event frequency and improve intravenous iron medication safety. Current domestic iron isomaltoside product labelling requires revision incorporating this contemporary real-world pharmacovigilance incidence data to accurately reflect routine clinical practice.

While external validity is limited by single-centre retrospective design, the matched case–control analytical framework strengthens reliability of the identified risk predictors. Future multicentre prospective pharmacovigilance studies collecting detailed infusion flow rate data are required to replicate these findings, interrogate underlying CARPA immunological mechanisms, and develop refined multi-variable risk stratification tools applicable across broader patient populations.

Declarations

Ethics approval and consent to participate

This retrospective pharmacovigilance study used fully de-identified routine electronic hospital medical records without additional patient contact or invasive testing. Formal institutional review board ethical approval was waived per institutional guidelines for non-interventional retrospective drug safety monitoring research. All raw clinical data were anonymised prior to extraction to eliminate all identifiable personal patient information, eliminating the requirement for written informed consent from individual participants.

Consent for publication

Not applicable, as all patient clinical data within this manuscript have been fully anonymised with no identifiable individual information included.

Availability of data and materials

The raw de-identified analytical dataset generated and analysed during the current retrospective study is available from the corresponding author upon reasonable formal written request. Restrictions apply to full hospital electronic medical record source data due to local hospital data privacy regulations.

Competing interests

All authors declare no financial, commercial, or non-financial competing interests related to the conception, execution, analysis, or publication of this pharmacovigilance research manuscript. No industry funding or pharmaceutical manufacturer support was received for this work.

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Authors' contributions

HC and QQF equally contributed to study design, data extraction and primary statistical analysis; YPL assisted with CHPS signal data sorting and literature retrieval; HWL supervised pharmacovigilance data quality control and manuscript revision; HWC supervised statistical methodology and final manuscript polishing. All authors read, critically revised, and provided final approval of the complete submitted manuscript, and accept full accountability for all components of the research work.

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Tables

Table 1 Clinical manifestations, vital sign changes and clinical interventions for patients with iron isomaltoside hypersensitivity reactions

No.	Age (Y)	Onset Time (Min)	Remission Time (Min)	Vital Signs			Clinical Manifestations	Interventions
				Pulse Rate (bpm)	Respiratory Rate (bpm)	Blood Pressure (SBP/DBP, mmHg)		
1	41	20	10	104	22	116/78	Disturbance in Respiration	Pause, then Ease off and Continue
2	46	6	20	74	20	117/70	Shortness of Breath, Chest Tightness, and Flushed Complexion	Pause, then Ease off and Continue
3	38	7	26	61	19	138/73	Facial Distension and Redness, Chest Tightness and Discomfort	Pause, then Ease off and Continue
4	34	13	30	69	19	122/61	Recurrent Chest Discomfort	Stop the Intravenous Infusion
5	40	69	120	74	20	117/64	Rashes on the face and all over the body, Itching and Dizziness	Stop the Intravenous Infusion
6	46	1	24	60	20	152/97	Generalized Distension and Pain	Pause, then Ease off and Continue
7	48	8	10	86	21	165/97	Difficulty in Breathing and Flushed Complexion	Administer Dexamethasone by Intravenous Push, and Stop the Infusion
8	31	25	23	105	20	151/98	Flushed Face, Profuse Sweating, Nausea and Vomiting, General Weakness, Chest Tightness, and Numbness in the face	Administer Dexamethasone by Intravenous Push, and Stop the Infusion
9	40	10	10	92	20	161/91	Flushed Face, Headache and Nausea	Pause, then Ease off and Continue

10	48	12	17	71	20	106/80	Flushed Face, Nausea, Vomiting and Palpitations	Administer Dexamethasone by Intravenous Push, and Stop the Infusion
11	32	16	73	69	20	101/67	Itching and Rashes on the face and the right upper limb	Administer Dexamethasone by Intravenous Push, then Ease off and Continue
12	41	111	95	100	22	116/74	Cough	Pause, then Ease off and Continue
13	49	10	6	87	20	106/69	Unnerved	Pause, then Ease off and Continue
14	58	15	19	78	23	189/89	Chest Tightness, Shortness of Breath and Flushed Complexion	Stop the Intravenous Infusion
15	41	42	30	74	20	122/70	Dizziness, Nausea and Discomfort	Pause, then Ease off and Continue
16	42	20	8	87	20	112/72	Chest Pain	Pause, then Ease off and Continue
17	42	9	40	78	20	124/76	Paralyzed Hands, Difficulty in Breathing	Pause, then Ease off and Continue
18	43	5	170	94	18	111/66	Extensive Severe Itching all over the body	Administer Dexamethasone by Intravenous Push, and Stop the Infusion
19	43	124	111	76	20	99/65	Itchy Skin Accompanied by Wheals	Administer Dexamethasone by Intravenous Push, then Ease off and Continue
20	46	3	5	89	22	145/76	Feeling hot all over, Chest Tightness, Difficulty in Breathing, Flushed all over the body, Severe Itching	Administer Dexamethasone by Intravenous Push, and Stop the Infusion
21	44	37	41	97	20	121/79	Throat Tight	Pause, then Ease off and

								Continue
22	47	14	60	75	20	136/62	Chest Tightness, Shortness of Breath, Convulsions	Stop the Intravenous Infusion
23	50	38	40	82	20	125/68	Generalized Itching, Redness of the Skin with Papular Lumps, Facial Rashes, Nausea, Vomiting	Administer Dexamethasone by Intravenous Push, then Ease off and Continue
24	50	5	8	80	32	162/93	Difficulty in Breathing, Numbness in the Lips, Flushed Complexion, Dizziness and Discomfort.	Administer Dexamethasone by Intravenous Push, and Stop the Infusion
25	54	45	30	82	20	106/76	Extensive Red Rashes on the Skin of the Limbs, Accompanied by Itching	Administer Dexamethasone by Intravenous Push, then Ease off and Continue
26	40	14	13	110	21	116/77	Chest Tightness	Stop the Intravenous Infusion
27	67	5	10	106	21	135/78	Palpitations, Back Pain	Pause, then Ease off and Continue

Table 2 Baseline demographic, clinical and laboratory characteristics between matched case and control groups

Observation Indicators	The Case Group(n=27)	The Control Group(n=108)	Statistics	P-value
Demographic characteristics				
Age（y，$\bar{x}\pm s$）	44.48 ± 7.60	45.02 ± 7.78	t=0.32	0.748
BMI（kg/m²，$\bar{x}\pm s$）	23.55 ± 3.19	23.46 ± 3.20	t=-0.13	0.897
Chronic Diseases［n（%）］	8 (29.63)	12 (11.11)	χ^2=4.49	0.034
Allergies［n（%）］	2 (7.41)	5 (4.63)	χ^2=0.01	0.923
Blood Transfusion History［n（%）］	2 (7.41)	14 (12.96)	χ^2=0.22	0.641
Duration of Primary Disease［n（%）］			χ^2=4.62	0.032
＞5 Years	2 (7.41)	29 (26.85)		
≤5 Years	25 (92.59)	79 (73.15)		
Medication-Related Parameters				
Contraction Hormone Combination［n（%）］	7 (25.93)	25 (23.15)	χ^2=0.09	0.761
Combine Antibiotics［n（%）］	15 (55.56)	34 (31.48)	χ^2=5.41	0.020
Dosage of Medication（mg）［n（%）］			χ^2=0.00	1.000
500	2 (7.41)	10 (9.26)		
1000	25 (92.59)	98 (90.74)		
Medication Time［n（%）］			χ^2=3.66	0.056
Postoperative Use	11 (40.74)	66 (61.11)		
Preoperative Use	16 (59.26)	42 (38.89)		
Post-Configuration Time[min，M (Q_1, Q_3)]	107 (86, 140)	125 (91, 169)	Z=-1.13	0.258
Baseline Laboratory Tests				
Electrocardiographic Abnormality［n（%）］	9 (33.33)	17 (15.74)	χ^2=4.30	0.038
WBC[$\times10^9$/L，M (Q_1, Q_3)]	6.15 (5.60, 8.24)	7.50 (5.71, 10.38)	Z=-1.44	0.150
RBC，$\times10^{12}$/L，$\bar{x}\pm s$）	3.69 ± 0.63	3.57 ± 0.70	t=-0.79	0.430
LY，$\times10^9$/L，$\bar{x}\pm s$）	1.32 ± 0.36	1.36 ± 0.46	t=0.42	0.676
NE[$\times10^9$/L，M (Q_1, Q_3)]	4.44 (3.59, 6.28)	5.44 (3.72, 8.24)	Z=-1.34	0.181
PLT[$\times10^9$/L，M (Q_1, Q_3)]	294.00 (258.50, 374.00)	266.50 (208.00, 335.25)	Z=-2.16	0.031
HGB(g/L，$\bar{x}\pm s$）	76.15 ± 10.70	85.28 ± 14.33	t=3.10	0.002
AST [U/L，M(Q_1, Q_3)]	18.50 (15.45, 22.80)	19.30 (16.00, 22.75)	Z=-0.43	0.666

ALT [U/L，M(Q_1, Q_3)]	11.20 (8.65, 14.35)	12.75 (10.95, 18.70)	Z=-2.05	0.041
TBIL[umol/L，M(Q_1, Q_3)]	8.00 (6.20, 11.10)	8.70 (6.97, 11.15)	Z=-0.78	0.436
DBIL[umol/L，M(Q_1, Q_3)]	1.30 (1.05, 1.95)	1.60 (1.20, 2.32)	Z=-1.41	0.158
NBIL[umol/L，M(Q_1, Q_3)]	6.80 (4.75, 9.05)	6.90 (5.30, 8.55)	Z=-0.24	0.813
CRE(umol/L，$\bar{x}\pm s$)	56.19 ± 10.21	54.84 ± 14.19	t=-0.46	0.644
CK[U/L，M(Q_1, Q_3)]	52.00 (46.00, 68.50)	60.50 (48.75, 85.25)	Z=-1.68	0.093

Table 3 Multivariate binary logistic regression analysis of independent risk factors for iron isomaltoside-associated hypersensitivity reactions

Observation Indicators	**β**	**S.E**	**Z**	**P**	**OR (95%CI)**
Chronic Diseases	1.20	0.64	1.89	0.058	3.33 (0.96 ~ 11.57)
Duration of Primary Disease	1.51	0.91	1.66	0.096	4.52 (0.77 ~ 26.74)
Electrocardiographic Abnormality	0.68	0.60	1.14	0.255	1.98 (0.61 ~ 6.38)
Combine Antibiotics	1.48	0.57	2.60	0.009	4.38 (1.44 ~ 13.36)
PLT	0.01	0.00	2.59	0.010	1.01 (1.01 ~ 1.01)
HGB	-0.06	0.02	-2.84	0.005	0.94 (0.91 ~ 0.98)
ALT	-0.01	0.02	-0.72	0.469	0.99 (0.95 ~ 1.03)