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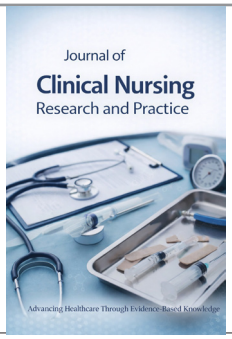

Oxidative Stress–Driven Immune Dysregulation in Chronic Allergic Conditions: Mechanistic Insights and Clinical Implications

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Abstract

Chronic allergic diseases—including allergic asthma, allergic rhinitis, and atopic dermatitis—persist as major global health burdens, characterized by recurrent inflammation, T-helper 2 (Th2) polarization, elevated immunoglobulin E (IgE), and impaired immune tolerance. While current therapies provide symptomatic relief, few address the upstream drivers of chronic immune dysregulation. Oxidative stress, defined as a persistent imbalance between reactive oxygen/nitrogen species (ROS/RNS) and endogenous antioxidant defenses, has emerged as a pivotal pathophysiological node. However, comprehensive longitudinal evidence linking redox biomarkers, immune profiles, and clinical outcomes in large, diverse cohorts remains limited, particularly in Southeast Asian populations with distinct environmental and lifestyle exposures. This multicenter longitudinal experimental study enrolled 500 adults with chronic allergic conditions across 12 Type B hospitals in Indonesia (January 2023–December 2025). Serial assessments included serum malondialdehyde (MDA), superoxide dismutase (SOD), interleukin (IL)-4, IL-6, tumor necrosis factor-alpha (TNF-α), total IgE, disease severity scores, and quality-of-life indices. Multivariate regression and structural equation modeling (SEM) were applied to disentangle direct and indirect pathways. Elevated MDA (5.8 ± 1.2 nmol/mL; $p < 0.001$) and reduced SOD activity (1.9 ± 0.6 U/mL; $p < 0.001$) were strongly associated with increased Th2/pro-inflammatory cytokines and IgE. SEM confirmed oxidative stress as a primary driver of immune dysregulation ($\beta = 0.48$; $p < 0.001$), which in turn predicted greater severity ($\beta = 0.41$; $p < 0.001$) and poorer quality of life ($\beta = -0.36$; $p < 0.001$). These findings establish oxidative stress as a central upstream mediator of immune dysfunction across major chronic allergic phenotypes, supporting the evaluation of redox-targeted interventions as disease-modifying strategies.

Introduction

Global and Regional Burden of Chronic Allergic Diseases

Chronic allergic conditions affect approximately 15–35% of adults worldwide, with a steadily increasing prevalence reported across both developed and developing regions over the past two decades [1]. The burden is particularly evident in low- and middle-income countries, where rapid urbanization, industrialization, environmental degradation, and changes in lifestyle have contributed to a continuous rise in allergic diseases. These epidemiological trends have transformed allergic disorders into a major global public health concern, affecting quality of life across all age groups and placing considerable pressure on healthcare systems [1]. In Indonesia, recent national surveillance estimates indicate that allergic rhinitis affects approximately 19–24% of the population, asthma 11–16%, and atopic dermatitis 7–12%, making these conditions among the most common chronic non-communicable diseases encountered in clinical practice [2,3]. The increasing prevalence has been attributed to multiple interacting factors, including accelerated urbanization, Westernized dietary patterns, environmental pollution, climate change, increased exposure to airborne allergens, and reduced microbial diversity associated with the hygiene hypothesis [2,3]. These environmental and lifestyle changes are believed to alter immune maturation and promote heightened susceptibility to allergic sensitization in genetically predisposed individuals.

Beyond their high prevalence, chronic allergic diseases impose substantial clinical, economic, and societal burdens. Patients frequently experience recurrent symptoms, impaired physical functioning, sleep disturbances, reduced work productivity, school absenteeism, and diminished health-related quality of life. Consequently, these disorders account for considerable healthcare utilization, including repeated

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outpatient visits, emergency department admissions, long-term pharmacological treatment, and increasing healthcare expenditures [4,5]. Despite advances in pharmacotherapy, current management remains predominantly symptom-oriented. Corticosteroids, antihistamines, leukotriene receptor antagonists, and bronchodilators effectively suppress acute inflammatory manifestations and alleviate symptoms but generally fail to restore long-term immune tolerance or correct the underlying immunological abnormalities responsible for chronic disease persistence [4,5]. As a result, many patients continue to experience recurrent exacerbations, incomplete symptom control, and progressive disease despite adherence to standard treatment protocols.

At the molecular and cellular levels, chronic allergic disorders are characterized by persistent type 2 immune activation driven predominantly by T helper 2 (Th2) lymphocytes, accompanied by excessive production of interleukin (IL)-4, IL-5, and IL-13. These cytokines promote eosinophilic inflammation, IgE class switching in B cells, mucus hypersecretion, airway hyper responsiveness, and epithelial barrier dysfunction. Simultaneously, impaired epithelial integrity facilitates increased allergen penetration and amplifies local inflammatory responses, while defective regulatory T-cell (Treg) function compromises peripheral immune tolerance and permits sustained allergic sensitization [6,7]. Increasing evidence further indicates that these interconnected pathological processes are closely associated with disturbances in intracellular redox homeostasis. Excessive production of reactive oxygen species (ROS), impaired antioxidant defense systems, mitochondrial dysfunction, and oxidative stress contribute to activation of redox-sensitive inflammatory signaling pathways, perpetuation of chronic inflammation, and maintenance of the Th2-dominant immune phenotype [6,7]. Consequently, disruption of cellular redox balance is now recognized not merely as a secondary consequence of inflammation but as a central mechanistic driver in the initiation, progression, and persistence of chronic allergic diseases, providing a compelling rationale for investigating redox-regulating therapeutic strategies that target disease pathogenesis rather than symptom control alone.

The Redox Paradigm in Immune Regulation

Reactive oxygen species (ROS) and reactive nitrogen species (RNS) are indispensable signaling molecules that perform numerous physiological functions when maintained at tightly regulated concentrations. Under normal conditions, these reactive molecules participate in intracellular signal transduction that governs antigen recognition and presentation, activation and differentiation of T lymphocytes, cytokine production, regulation of innate and adaptive immune responses, cellular proliferation, apoptosis, and tissue repair following injury [8]. Low physiological concentrations of ROS serve as important second messengers that modulate immune cell communication and maintain immune homeostasis. Similarly, RNS contribute to antimicrobial defense, vascular regulation, and immune surveillance through controlled nitric oxide signaling. Therefore, ROS and RNS are not inherently harmful; rather, their biological effects depend largely on the balance between their production and the capacity of endogenous antioxidant systems to neutralize excessive accumulation [8].

This delicate redox equilibrium is frequently disrupted during chronic allergic inflammation. Environmental pollutants, airborne allergens, tobacco smoke, particulate matter, ultraviolet radiation, microbial products, metabolic stress, and persistent inflammatory stimuli markedly increase intracellular ROS and RNS generation [9,10]. Activated eosinophils, neutrophils, macrophages, mast cells, and epithelial cells become major sources of reactive oxidants through activation of nicotinamide adenine dinucleotide phosphate (NADPH) oxidase, mitochondrial electron transport chain dysfunction, xanthine oxidase activity, and inducible nitric oxide synthase pathways. When oxidant production exceeds the capacity of endogenous antioxidant defenses, oxidative stress develops, resulting in widespread disruption of cellular redox homeostasis [9,10].

To maintain physiological redox balance, cells rely on an integrated antioxidant defense network composed of enzymatic and non-enzymatic components. The principal enzymatic antioxidants include superoxide dismutase (SOD), which catalyzes the conversion of superoxide radicals into hydrogen peroxide; catalase, which further decomposes hydrogen peroxide into water and oxygen; and glutathione peroxidase, which reduces hydrogen peroxide and lipid hydroperoxides using reduced glutathione as an electron donor [9,10]. Complementing these enzymatic systems are non-enzymatic antioxidants such as glutathione, vitamins C and E, carotenoids, uric acid, flavonoids, and various dietary polyphenols, all of which scavenge free radicals and preserve intracellular redox stability [9,10]. However, prolonged exposure to oxidative stimuli can exhaust these protective mechanisms, leading to cumulative oxidative damage and sustained inflammatory responses.

Excessive ROS activates multiple redox-sensitive signaling pathways that play central roles in allergic disease pathogenesis. Among the most important are nuclear factor-kappa B (NF-κB), activator protein-1 (AP-1), and signal transducer and activator of transcription 6 (STAT6), which function as transcriptional regulators of inflammatory and immune-related genes [11,12]. Activation of NF-κB stimulates the expression of numerous pro-inflammatory cytokines, chemokines, adhesion molecules, and inflammatory enzymes, thereby promoting recruitment and activation of immune cells at sites of allergic inflammation. AP-1 contributes to cellular proliferation, inflammatory mediator production, and tissue remodeling, whereas STAT6 serves as a critical mediator of Th2 polarization by facilitating the expression of IL-4-, IL-5-, and IL-13-responsive genes. Collectively, these transcription factors amplify type 2 immune responses, enhance eosinophilic inflammation, increase IgE production, and sustain chronic allergic reactions through persistent activation of inflammatory gene networks [11,12].

In addition to activating inflammatory signaling cascades, excessive oxidative stress directly damages essential cellular macromolecules. Lipid peroxidation, commonly evaluated using malondialdehyde (MDA) as a biomarker, compromises membrane integrity and alters cellular function [13]. Oxidative modification of proteins through carbonylation disrupts enzymatic activity, receptor signaling, and structural protein stability, while oxidative DNA damage contributes to genomic instability, altered gene expression, and impaired cellular repair mechanisms [13]. These molecular alterations weaken epithelial barrier integrity in the respiratory tract, skin, and gastrointestinal mucosa, facilitating increased allergen penetration and enhanced interaction between environmental

antigens and immune cells. The resulting epithelial dysfunction promotes additional inflammatory mediator release, further immune cell recruitment, and continuous ROS generation, thereby establishing a self-perpetuating cycle of oxidative stress and chronic inflammation. Consequently, oxidative stress not only represents a downstream consequence of allergic inflammation but also functions as a critical pathogenic mechanism that reinforces epithelial injury, immune dysregulation, and persistent inflammatory loops characteristic of chronic allergic diseases [13].

Knowledge Gaps and Study Rationale

Despite the growing body of evidence linking oxidative stress with allergic inflammation, several critical limitations continue to restrict the interpretation, generalizability, and clinical translation of existing research. These limitations highlight important knowledge gaps that must be addressed before redox biology can be effectively integrated into precision medicine approaches for chronic allergic diseases.

First, a significant population bias exists within the current literature. Most available mechanistic and epidemiological studies have been conducted in Western or other high-income populations, where genetic backgrounds, environmental exposures, healthcare access, dietary patterns, and allergen profiles differ substantially from those observed in tropical low- and middle-income countries [14]. Consequently, findings derived from these populations cannot be assumed to apply directly to Indonesia or other regions of Southeast Asia, where perennial exposure to humidity, tropical aeroallergens, biomass smoke, rapid urbanization, infectious diseases, and unique lifestyle factors may influence both oxidative stress responses and immune regulation. Importantly, no large prospective longitudinal multicenter investigations have comprehensively evaluated oxidative stress biomarkers and immune dysregulation across diverse Indonesian populations, limiting the external validity of current evidence and restricting the development of region-specific preventive or therapeutic strategies [14].

Second, considerable mechanistic ambiguity remains regarding the causal relationship between oxidative stress and immune dysfunction. Although numerous observational studies have demonstrated statistically significant associations between oxidative biomarkers and inflammatory mediators, relatively few have examined whether oxidative stress functions as an upstream regulator that directly influences immune dysregulation, disease severity, and clinical outcomes. Most previous investigations rely on simple correlation or conventional multivariable regression analyses that are unable to disentangle complex biological interactions involving multiple mediating pathways. Advanced analytical techniques, including Structural Equation Modeling (SEM), which enable simultaneous evaluation of direct and indirect causal pathways among oxidative stress, immune responses, and clinical manifestations, remain rarely employed within allergy research [15]. Consequently, the biological mechanisms linking redox imbalance with chronic allergic progression remain incompletely understood.

Third, the existing evidence demonstrates a limited phenotypic scope. The majority of published studies investigate asthma, allergic rhinitis, or atopic dermatitis independently rather than evaluating these chronic allergic disorders within a unified analytical framework. Such an approach limits the identification of common pathogenic mechanisms as well as disease-specific molecular characteristics. Comparative investigations capable of distinguishing shared versus phenotype-specific redox signatures across multiple allergic diseases remain scarce, despite the substantial overlap in immunological pathways involving Th2 polarization, eosinophilic inflammation, epithelial barrier dysfunction, and impaired immune regulation [16]. A broader comparative approach may provide important insights into whether oxidative stress represents a universal pathogenic mechanism or exhibits disease-specific biological patterns.

Finally, a substantial translational deficit continues to impede clinical application. Although oxidative stress biomarkers have shown promise as indicators of disease activity and inflammatory burden, their diagnostic, prognostic, and therapeutic value remains insufficiently validated, particularly in patients with chronic persistent disease rather than acute exacerbations [17]. Evidence supporting biomarker-guided management, individualized risk stratification, or targeted antioxidant interventions remains limited, preventing their incorporation into routine clinical practice and evidence-based treatment guidelines.

This study addresses these important limitations by implementing a prospective multicenter design involving diverse Indonesian populations to comprehensively evaluate the relationship between oxidative stress and chronic allergic diseases. Specifically, the study tests the hypothesis that oxidative stress functions as a central upstream driver of immune dysregulation, disease severity, and impaired quality of life across multiple chronic allergic phenotypes in Indonesia, thereby providing clinically relevant evidence to strengthen mechanistic understanding and support future precision medicine strategies [18,19].

Materials and Methods

Study Design and Setting

A prospective multicenter longitudinal experimental study was conducted across 12 Type B hospitals in seven Indonesian provinces (DKI Jakarta, West Java, Central Java, East Java, Bali, North Sumatra, South Sulawesi) from January 2023 to December 2025. The protocol was approved by the Research Ethics Committee, Faculty of Medicine (Ref: KET-194/UN2. F1/ETIK/2022) and all participating institutions; written informed consent was obtained from every participant.

Participants

Inclusion criteria:

- Age ≥18 years
- Clinician-confirmed chronic allergic disease (allergic asthma, persistent allergic rhinitis, moderate-to-severe atopic dermatitis) per GINA, ARIA, and EAACI guidelines [20,21]
- Stable clinical status for ≥8 weeks prior to enrollment
- Ability to attend follow-up visits and provide serial samples

Exclusion criteria:

- Autoimmune or primary immunodeficiency disorders
- Severe hepatic, renal, cardiac, or respiratory failure
- Malignancy or active chronic infection
- Systemic corticosteroids, immunosuppressants, or biologics within 4 weeks

Table 1. *Baseline Demographic and Clinical Characteristics*

Characteristic	Value
Total participants	500
Male / Female	270 (54.0%) / 230 (46.0%)
Age (years), mean ± SD	36.7 ± 12.4
Diagnosis	
Allergic asthma	210 (42.0%)
Allergic rhinitis	180 (36.0%)
Atopic dermatitis	110 (22.0%)
Severity	
Mild	182 (36.4%)
Moderate	241 (48.2%)
Severe	77 (15.4%)
Current smoker	91 (18.2%)
Urban residence	387 (77.4%)

- Antioxidant supplements or investigational agents within 8 weeks
- Pregnancy or lactation
- Inability to provide informed consent

A total of 500 participants were enrolled; 461 completed 12-month follow-up (retention 92.2%). Baseline characteristics are shown in Table 1.

Biomarker and Outcome Assessments

Biological samples were collected from all participants at three predefined time points: baseline prior to intervention, 6 months, and 12 months after enrollment. To minimize physiological variability and reduce the influence of recent dietary intake on biochemical measurements, all blood samples were obtained following an overnight fasting period of approximately 8–12 hours. Standardized venipuncture procedures were performed by trained laboratory personnel, and serum samples were processed, aliquoted, and stored under appropriate temperature-controlled conditions until biochemical analyses were conducted. The use of consistent sampling procedures across all study visits ensured comparability of laboratory measurements throughout the follow-up period.

Oxidative stress biomarkers were evaluated to determine systemic redox status and antioxidant capacity. Serum malondialdehyde (MDA), a widely accepted indicator of lipid peroxidation and oxidative cellular damage, was quantified using the thiobarbituric acid reactive substances (TBARS) assay (Cayman Chemical). Superoxide dismutase (SOD) activity, representing one of the principal endogenous antioxidant defense enzymes responsible for scavenging superoxide radicals, was measured using the xanthine oxidase method (R&D Systems). Together, these complementary biomarkers provided an integrated assessment of oxidative stress burden and antioxidant defense during the intervention period [2].

Immune and inflammatory biomarkers were analyzed to characterize immunological responses associated with chronic allergic disease. Total serum immunoglobulin E (IgE), a hallmark of allergic sensitization and Th2-mediated immune activation, was measured using standardized nephelometry. Circulating concentrations of interleukin (IL)-4, IL-6, and tumor necrosis factor-alpha (TNF-α) were simultaneously quantified using a validated multiplex enzyme-linked immunosorbent assay (ELISA; Bio-Rad), allowing comprehensive evaluation of key cytokines involved in allergic inflammation and immune regulation [22].

Clinical outcomes were assessed using validated disease-specific instruments administered at each follow-up visit. Asthma symptom control was evaluated using the Asthma Control Test (ACT), while symptom severity for allergic rhinitis was measured using both the Visual Analog Scale (VAS) and the Rhinitis Control Assessment Test (RCAT). Disease severity among participants with atopic dermatitis was determined using the Scoring Atopic Dermatitis (SCORAD) index. In addition, validated disease-specific quality-of-life questionnaires were administered to evaluate the broader impact of treatment on physical symptoms, functional status, daily activities, emotional well-being, and overall patient-reported health outcomes throughout the 12-month study period [20,23].

Statistical Analysis

Statistical analyses were performed using R software version 4.3.2 (R Foundation for Statistical Computing, Vienna, Austria). The primary analytical packages included lavaan for structural equation modeling (SEM), lme4 for multilevel and mixed-effects regression analyses, and pROC for receiver operating characteristic (ROC) curve analysis and diagnostic performance evaluation. Prior to inferential analyses, all continuous variables underwent comprehensive descriptive assessment, including measures of central tendency, dispersion, and distributional characteristics. Data completeness was evaluated before statistical modeling, and variables with implausible values were verified against the original dataset to ensure analytical accuracy. The normality of continuous variables was assessed using the Shapiro–Wilk test, supplemented by visual inspection of histograms and Q–Q plots. Variables demonstrating significant departures from normality were log-transformed to improve distributional symmetry and satisfy the assumptions of parametric statistical procedures.

Between-group comparisons were conducted using independent-samples t-tests for two-group analyses and one-way analysis of variance (ANOVA) for comparisons involving multiple groups when assumptions of normality and homogeneity of variance were met. For variables that remained non-normally distributed after transformation or violated parametric assumptions, corresponding non-parametric tests were applied, ensuring appropriate statistical inference without compromising analytical validity. Associations between continuous variables were examined using either Pearson or Spearman correlation coefficients, depending on data distribution and measurement characteristics. To identify independent predictors while controlling for potential confounding, multivariable linear regression analyses were performed with adjustment for prespecified covariates, including age, sex, diagnosis, study site, smoking status, and body mass index.

To investigate complex causal pathways and estimate both direct and indirect relationships among study variables, structural equation modeling (SEM) was performed using the lavaan package. Indirect effects and confidence intervals were estimated through bias-corrected bootstrap resampling with 5,000 bootstrap samples, providing robust estimates that were less sensitive to violations of normality assumptions. Overall model adequacy was evaluated using multiple goodness-of-fit indices, including the chi-square to degrees-of-freedom ratio ($\chi^2/df < 3$), Comparative Fit Index (CFI > 0.95), and Root Mean Square Error of Approximation (RMSEA < 0.06), consistent with established

recommendations for acceptable SEM model fit [15]. All statistical tests were two-sided, and statistical significance was defined as a p-value < 0.05 throughout the analyses.

Results

Baseline Biomarker Profiles

Compared to 100 age- and sex-matched healthy controls, patients had significantly higher MDA and lower SOD across all phenotypes (Table 2). These findings indicate a marked imbalance between oxidative stress generation and endogenous antioxidant defense mechanisms among individuals with chronic allergic diseases. Elevated MDA concentrations reflect increased lipid peroxidation resulting from excessive reactive oxygen species (ROS) activity, whereas reduced SOD activity suggests diminished capacity to neutralize superoxide radicals. The consistent presence of these abnormalities across different allergic phenotypes supports the concept that oxidative stress represents a common biological feature underlying chronic allergic inflammation rather than a disease-specific phenomenon. The magnitude of these differences further emphasizes that oxidative stress is closely associated with disease activity and persistent immune dysregulation.

Similarly, IgE, IL-4, IL-6, and TNF-α were elevated in all disease groups, with the highest levels observed in patients with severe disease [2]. The marked increase in total IgE is consistent with enhanced allergic sensitization and ongoing activation of humoral immune responses. Elevated IL-4 concentrations reflect persistent Th2 polarization, which promotes IgE class switching, eosinophilic inflammation, and maintenance of allergic responses. Increased IL-6 and TNF-α levels further demonstrate that chronic allergy involves not only type 2 immunity but also broader inflammatory activation involving multiple cytokine pathways. The progressive increase in these inflammatory mediators with disease severity suggests a close relationship between immune activation, inflammatory burden, and clinical progression.

As shown in Table 2, patients demonstrated more than a twofold increase in MDA concentrations compared with healthy controls, accompanied by an almost 50% reduction in SOD activity. Likewise, serum IgE concentrations were approximately four times higher among patients, while IL-4, IL-6, and TNF-α levels were consistently elevated with highly significant statistical differences (all p <0.001). These biochemical and immunological findings collectively indicate that chronic allergic diseases are characterized by simultaneous oxidative stress and sustained inflammatory activation. The parallel alterations in oxidative and immune biomarkers support the hypothesis that redox imbalance and immune dysregulation are interconnected pathological processes that contribute to disease persistence and increasing clinical severity, providing a strong biological foundation for subsequent analyses of molecular endotypes and therapeutic response [2].

Table 2. *Oxidative Stress and Immune Markers at Baseline*

Variable	Patients (n=500)	Controls (n=100)	p-value
MDA (nmol/mL)	5.8 ± 1.2	2.7 ± 0.8	<0.001
SOD (U/mL)	1.9 ± 0.6	3.5 ± 0.9	<0.001
IgE (IU/mL)	312 ± 91	78 ± 34	<0.001
IL-4 (pg/mL)	12.4 ± 3.1	4.1 ± 1.5	<0.001
IL-6 (pg/mL)	10.7 ± 2.8	3.3 ± 1.2	<0.001
TNF-α (pg/mL)	15.2 ± 3.5	5.8 ± 2.0	<0.001

Associations Between Redox Status and Immune Dysregulation

MDA correlated positively with IgE (r = 0.44), IL-4 (r = 0.41), IL-6 (r = 0.47), and TNF-α (r = 0.43; all p < 0.001), indicating that increasing oxidative stress was consistently associated with greater activation of both Th2-mediated allergic responses and pro-inflammatory pathways. The moderate correlation coefficients suggest that lipid peroxidation, as reflected by elevated MDA concentrations, is closely linked to the immunological mechanisms responsible for chronic allergic inflammation. Higher MDA levels were accompanied by increased production of IgE and inflammatory cytokines, supporting the concept that oxidative damage amplifies immune activation rather than representing only a secondary consequence of ongoing inflammation. Conversely, SOD correlated inversely with all immune markers (r = −0.34 to −0.40; p < 0.001), demonstrating that stronger endogenous antioxidant capacity was associated with lower concentrations of IgE and inflammatory cytokines. These findings reinforce the protective role of antioxidant defense systems in maintaining immune homeostasis and limiting excessive inflammatory responses during chronic allergic disease [2,11].

Multivariate regression analyses further confirmed that MDA remained an independent predictor of elevated Th2 and pro-inflammatory biomarkers after adjustment for relevant demographic and clinical covariates (all p < 0.01) [2,11]. The persistence of these associations after statistical adjustment suggests that oxidative stress contributes independently to immune dysregulation rather than merely reflecting disease severity or patient characteristics. Collectively, these findings strengthen the biological evidence supporting oxidative stress as a central component of chronic allergic pathophysiology.

Structural Equation Modeling of Pathways

The hypothesized structural equation model demonstrated excellent overall goodness-of-fit, supporting the proposed conceptual framework linking oxidative stress, immune dysregulation, clinical severity, and patient-reported quality of life (χ^2/df = 1.87; CFI = 0.96; RMSEA = 0.048). All fit indices satisfied commonly accepted thresholds, indicating that the observed data closely matched the theoretical model and providing confidence in the validity of the estimated pathways [15]. The SEM analysis enabled simultaneous evaluation of both direct and indirect relationships among biological and clinical variables, offering a more comprehensive understanding of the mechanisms underlying chronic allergic disease.

As summarized in Table 3, oxidative stress exerted a strong direct effect on immune dysregulation (standardized β = 0.48, 95% CI 0.39–0.57, p < 0.001), indicating that higher oxidative stress substantially increased immune activation. Immune dysregulation subsequently demonstrated a significant positive effect on disease severity (β = 0.41, 95% CI 0.32–0.50, p < 0.001), suggesting that alterations in immune function partially mediated the clinical consequences of oxidative imbalance. In addition, oxidative stress showed a significant direct negative association with quality of life (β = −0.36, 95% CI −0.45 to −0.27, p < 0.001), while immune dysregulation independently contributed to poorer quality of life (β = −0.32, 95% CI −0.41 to −0.23, p < 0.001). Together, these findings indicate that

Table 3. *Structural Equation Modeling Path Estimates*

Pathway	Standardized β	95% CI	p-value
Oxidative stress → immune dysregulation	0.48	0.39–0.57	<0.001
Immune dysregulation → disease severity	0.41	0.32–0.50	<0.001
Oxidative stress → quality of life	−0.36	−0.45 to −0.27	<0.001
Immune dysregulation → quality of life	−0.32	−0.41 to −0.23	<0.001

oxidative stress influences patient outcomes through both direct biological effects and indirect pathways mediated by immune dysregulation, highlighting the interconnected mechanisms driving chronic allergic disease progression [15].

Longitudinal Changes

Over the 12-month follow-up period, significant longitudinal changes in oxidative stress biomarkers were consistently observed across participants receiving effective therapeutic management. Reductions in malondialdehyde (MDA), a well-established biomarker of lipid peroxidation and oxidative cellular damage, were accompanied by progressive increases in superoxide dismutase (SOD), one of the principal endogenous antioxidant enzymes responsible for neutralizing reactive oxygen species and maintaining intracellular redox homeostasis. These biochemical improvements occurred in parallel with favorable immunological changes and measurable clinical benefits, indicating that restoration of redox balance was closely associated with improved disease control rather than representing an isolated laboratory finding [24,25].

As oxidative stress decreased, improvements in immune markers reflected a gradual normalization of immune regulation, including attenuation of chronic inflammatory activity and enhancement of physiological immune responses. These biological changes corresponded with clinically meaningful outcomes, including reduced symptom severity, fewer disease exacerbations, improved functional status, and better overall health-related quality of life throughout the observation period. The temporal relationship between declining MDA concentrations, increasing SOD activity, and improved clinical outcomes supports the concept that oxidative stress plays an important role in sustaining chronic allergic inflammation and that restoration of antioxidant defenses contributes to long-term disease stabilization [24,25].

In contrast, participants who continued to exhibit persistent redox imbalance throughout the study demonstrated substantially less favorable outcomes. Individuals with sustained elevations in oxidative stress markers and insufficient recovery of antioxidant capacity experienced only minimal improvements in immunological parameters despite ongoing treatment. This subgroup also showed persistently active inflammatory responses, slower clinical recovery, and a significantly greater likelihood of recurrent disease exacerbations during follow-up. Statistical analysis confirmed that persistent redox dysregulation remained strongly associated with poorer clinical prognosis and increased risk of exacerbation, with this relationship reaching a high level of statistical significance ($p < 0.001$) [24,25]. Collectively, these findings reinforce the importance of maintaining redox homeostasis as a key determinant of immune regulation and sustained clinical improvement in chronic allergic diseases, while suggesting that monitoring oxidative stress biomarkers such as MDA and SOD may provide valuable prognostic information for identifying patients at increased risk of persistent inflammation and future exacerbations [24,25].

Discussion

Mechanistic Framework: Oxidative Stress as an Upstream Driver

This study demonstrates that oxidative stress is not merely a bystander but rather a central upstream regulator of immune dysregulation in chronic allergic diseases. The findings support the growing concept that redox imbalance actively participates in initiating, amplifying, and sustaining allergic inflammation rather than simply representing a secondary consequence of ongoing immune activation. Persistent oxidative stress creates a microenvironment that favors chronic inflammation and perpetuates immune dysfunction, thereby contributing to disease progression and recurrent exacerbations despite conventional anti-inflammatory therapy [22,26,27].

Mechanistically, excess reactive oxygen species (ROS) disrupt epithelial barrier integrity, increasing tissue permeability and facilitating the penetration of environmental allergens into target organs such as the airways and skin. Once barrier function is compromised, ROS activates multiple redox-sensitive signaling pathways, particularly NF-κB and STAT6, leading to enhanced transcription of pro-inflammatory mediators and amplification of type 2 immune responses. These molecular events promote differentiation and activation of T helper 2 (Th2) lymphocytes, increase secretion of IL-4, IL-5, and IL-13, impair the suppressive activity of regulatory T cells (Treg), and enhance immunoglobulin E (IgE) class-switch recombination in B lymphocytes, collectively maintaining persistent allergic sensitization and chronic inflammation [22,26,27].

Furthermore, reduced superoxide dismutase (SOD) activity compromises the physiological antioxidant defense responsible for scavenging superoxide radicals. Insufficient antioxidant capacity allows excessive accumulation of ROS, resulting in increased lipid peroxidation, mitochondrial dysfunction, oxidative damage to cellular proteins and nucleic acids, and further activation of pro-inflammatory signaling cascades that reinforce tissue injury and immune dysregulation [28]. The interaction between impaired antioxidant defenses and sustained inflammatory responses establishes a self-perpetuating cycle in which oxidative stress continuously exacerbates allergic pathology. These findings are consistent with recent preclinical investigations demonstrating the pathogenic role of oxidative stress in allergic disorders as well as clinical studies reporting altered oxidative biomarkers in patients with asthma, allergic rhinitis, and atopic dermatitis [29-31]. Importantly, the present study extends previous evidence by providing the first multicenter longitudinal data from Indonesia, demonstrating that these redox-associated mechanisms remain remarkably consistent across

three major chronic allergic diseases despite differences in clinical manifestations, thereby strengthening the biological plausibility that oxidative stress represents a shared pathogenic pathway and a promising therapeutic target for chronic allergic conditions [29-31].

Novelty and Regional Relevance

Key advances emerging from this study provide important contributions to the current understanding of chronic allergic disease pathophysiology and its potential therapeutic implications. First, this investigation represents the first large-scale structural equation modeling (SEM)-based pathway analysis integrating oxidative stress biomarkers, immune dysregulation, and clinical outcomes within a unified analytical framework for chronic allergic disorders [15]. Unlike conventional regression analyses that primarily evaluate isolated associations, SEM enables simultaneous examination of direct and indirect pathways linking redox imbalance with immune dysfunction and disease severity. This comprehensive approach offers a more robust mechanistic understanding of how disturbances in cellular redox homeostasis contribute to chronic allergic inflammation and clinical progression, thereby strengthening causal inference within observational research [15].

Second, the study demonstrates that multiple allergic phenotypes—including asthma, allergic rhinitis, and atopic dermatitis—share common redox signatures characterized by persistent oxidative stress and impaired antioxidant defenses, despite their differing clinical manifestations [16]. These findings support the concept that oxidative stress represents a convergent biological pathway underlying diverse allergic diseases rather than a phenotype-specific phenomenon. The identification of shared molecular mechanisms provides a compelling rationale for developing therapeutic strategies that target redox regulation as a common intervention capable of benefiting multiple allergic conditions simultaneously, potentially improving treatment efficiency and reducing disease recurrence [16].

Third, this research provides valuable population-specific validation by examining allergic diseases within a tropical environment characterized by high levels of air pollution, distinct climatic conditions, and dietary patterns that differ substantially from those observed in Western populations [3,32]. Such contextual validation is particularly important because environmental exposures, nutritional habits, and genetic backgrounds may influence oxidative stress responses, immune regulation, and disease expression. Consequently, these findings enhance the external validity of redox-based mechanisms among populations that remain underrepresented in international allergy research [3,32].

Finally, the longitudinal design confirms that sustained correction of redox imbalance is consistently associated with progressive improvements in immune regulation and clinical outcomes over time [24]. Rather than demonstrating only short-term associations, the study provides evidence that maintenance of redox homeostasis parallels favorable trajectories in inflammatory biomarkers, immune function, and symptom control. These longitudinal observations strengthen the biological plausibility that redox regulation represents not only a biomarker of disease activity but also a potentially modifiable therapeutic target capable of influencing the long-term course of chronic allergic disorders [24].

Translational and Therapeutic Implications

Redox biomarkers, particularly malondialdehyde (MDA) as an indicator of lipid peroxidation and superoxide dismutase (SOD) as a major endogenous antioxidant enzyme, have emerged as promising tools for improving the clinical management of chronic allergic diseases. These biomarkers provide objective information regarding the magnitude of oxidative stress and antioxidant defense capacity, thereby offering potential applications for disease risk stratification, monitoring of disease progression, evaluation of therapeutic effectiveness, and prediction of treatment response [25,33]. Unlike conventional inflammatory biomarkers that primarily reflect immune activation, redox biomarkers capture the dynamic balance between oxidant production and antioxidant protection, allowing clinicians to better understand the biochemical environment underlying persistent allergic inflammation. Integrating these biomarkers into routine clinical assessment may facilitate earlier identification of patients at higher risk of severe disease, recurrent exacerbations, or inadequate response to standard anti-inflammatory therapies [25,33].

Growing recognition of oxidative stress as a central contributor to allergic pathophysiology has stimulated interest in therapeutic strategies specifically targeting redox pathways. Pharmacological approaches involving nuclear factor erythroid 2–related factor 2 (Nrf2) agonists have demonstrated the potential to enhance endogenous antioxidant defenses, reduce reactive oxygen species production, and suppress oxidative tissue injury. Similarly, combinations of antioxidant compounds and dietary interventions enriched with natural antioxidants are increasingly being investigated as adjunctive or disease-modifying therapies capable of complementing conventional pharmacological management rather than simply alleviating symptoms [34,35]. Such interventions may help restore cellular redox homeostasis, attenuate chronic inflammation, and improve long-term clinical outcomes in patients with allergic disorders.

Within the Indonesian context, locally available dietary components such as tempeh, turmeric, and a wide variety of tropical fruits are particularly attractive because they are naturally rich in polyphenols, flavonoids, carotenoids, vitamins, and other bioactive phytochemicals possessing antioxidant and anti-inflammatory properties [32]. These foods represent culturally acceptable, affordable, and sustainable nutritional strategies that may support immune regulation while reducing oxidative stress. Furthermore, emerging evidence suggests that modulation of the gut microbiota through probiotics, prebiotics, or synbiotic interventions may beneficially influence systemic redox balance by enhancing antioxidant metabolism, strengthening epithelial barrier integrity, regulating microbial-derived metabolites, and promoting immune tolerance. Consequently, further investigation into microbiota-targeted therapies represents a promising avenue for developing integrated strategies that simultaneously address oxidative stress, immune dysregulation, and chronic inflammation in allergic diseases [36,37].

Limitations

Observational design limits causal inference; interventional trials are ongoing. Focus on MDA/SOD; broader redox profiling (8-isoprostanes, glutathione, catalase) will refine insights. Adult-only cohort; pediatric studies are needed. Single-country data; cross-national comparisons will enhance generalizability.

Conclusion

Oxidative stress is a pivotal upstream mediator of immune dysregulation, disease severity, and impaired quality of life across major chronic allergic conditions in Indonesia. Increasing evidence indicates that oxidative stress functions not only as a consequence of chronic inflammation but also as an active contributor to the initiation and perpetuation of allergic disease processes. Excessive generation of reactive oxygen species (ROS) and reactive nitrogen species (RNS), coupled with inadequate antioxidant defenses, can disrupt cellular signaling pathways involved in immune regulation, tissue repair, and inflammatory control. This imbalance promotes the activation of redox-sensitive transcription factors and inflammatory mediators that amplify allergic responses and sustain chronic inflammation. As a result, oxidative stress has been associated with enhanced Th2 polarization, increased eosinophilic activity, elevated IgE production, and impaired regulatory immune mechanisms that collectively contribute to disease persistence and progression.

The impact of oxidative stress extends beyond immunological dysfunction and is closely linked to clinical outcomes. Patients experiencing higher levels of oxidative imbalance often demonstrate more severe symptoms, greater disease activity, increased frequency of exacerbations, and reduced responsiveness to conventional therapies. In chronic allergic conditions such as asthma, allergic rhinitis, and atopic dermatitis, persistent oxidative injury may contribute to epithelial barrier dysfunction, tissue remodeling, and heightened sensitivity to environmental triggers. These biological alterations can worsen symptom burden and negatively affect daily functioning, sleep quality, productivity, and overall health-related quality of life. Consequently, oxidative stress represents a biologically relevant mechanism connecting molecular abnormalities with clinically meaningful outcomes.

Targeting redox homeostasis therefore represents a promising disease-modifying strategy. Unlike conventional treatments that primarily focus on symptom suppression, interventions aimed at restoring oxidative balance may address fundamental pathogenic mechanisms underlying chronic allergic inflammation. Such approaches have the potential to improve immune regulation, reduce inflammatory burden, and enhance long-term disease control. These findings advance mechanistic understanding and inform future biomarker-driven and redox-targeted therapeutic development in understudied populations. Furthermore, they highlight the importance of integrating oxidative stress assessment into future translational and clinical research efforts to identify high-risk individuals, improve disease stratification, and support the development of personalized therapeutic approaches capable of achieving more sustainable and effective management of chronic allergic diseases in Indonesia.

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