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Blood-Based Inflammatory Biomarkers: A Literature Review

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ABSTRACT

Introduction: Inflammation is a fundamental biological response involved in the development and progression of various diseases and is commonly assessed using blood-based indicators. A wide range of inflammatory biomarkers has been described. However, differences in their biological characteristics and clinical relevance require a clear understanding for appropriate use. **Objective:** This review aims to summarize the blood-based inflammatory biomarkers and to present a clear description of their characteristics, strengths, and limitations, as well as key concepts related to their clinical application and interpretation as indicators of inflammatory activity. **Method:** This study was conducted as a literature review using secondary data from scientific publications. Articles published within the last five years (2021-2026) were identified from PubMed and Google Scholar and selected based on their relevance to blood-based inflammatory biomarkers and the clarity of reported information. The selected literature, consisting of original research articles and review papers, was analyzed descriptively to synthesize and compare findings across studies. **Result:** The results indicate that blood-based inflammatory biomarkers can be grouped into several main categories, each reflecting different mechanisms and stages of inflammation. Differences in biological function and applicability were observed among biomarker groups, highlighting variations in their utility across inflammatory contexts. **Conclusion:** Blood-based inflammatory biomarkers provide important information for evaluating inflammatory status. Accurate assessment depends on an interpretation that accounts for biological function, inflammatory context, and inherent limitations of each biomarker.

Keywords: biomarkers, blood-based biomarkers, inflammation

INTRODUCTION

Inflammation is a fundamental biological process activated in response to infection, tissue injury, or exposure to harmful stimuli. This process contributes to the maintenance of tissue integrity and physiological homeostasis through tightly regulated interactions between stromal cells and resident and recruited immune cells (Menzel et al., 2021; Raju et al., 2025). While acute inflammation is commonly associated with overt clinical signs, inflammatory activity may also persist in a chronic, low-grade systemic form. In such circumstances, inflammation often remains clinically silent while exerting cumulative adverse effects on long-term health outcomes (Menzel et al., 2021; Rasmussen et al., 2021).

Persistent inflammation has been linked to the initiation and progression of a wide range of pathological conditions, including cardiovascular disease, malignancies, metabolic disorders, autoimmune diseases, neurodegenerative conditions, and increased mortality risk across the lifespan (Rasmussen et al., 2021). The absence of distinct, easily identifiable clinical manifestations underscores the need for objective indicators to detect inflammatory burden at an early stage, support disease risk stratification, and monitor therapeutic responses. Accordingly, blood-derived biomarker panels have become increasingly important tools in prognostic assessment and clinical decision-making (Iordache et al., 2025; Menzel et al., 2021).

Blood-based biomarkers are particularly suitable for evaluating inflammatory status due to

the accessibility of blood sampling, the feasibility of repeated measurements, and compatibility with standardized laboratory procedures. These characteristics allow for continuous monitoring of inflammation in both clinical practice and research settings, thereby facilitating longitudinal assessment of disease progression and treatment response (Pah et al., 2025; Wunderle et al., 2025).

Advances in inflammation research have substantially expanded the range of measurable blood-based biomarkers. Individual markers capture different components of the inflammatory cascade, including acute-phase responses, cytokine and chemokine signaling, immune cell activation, leukocyte dynamics, and chronic low-grade inflammatory states associated with increased long-term health risk (Rasmussen et al., 2025; Visser et al., 2022; Walzik et al., 2021; Liu et al., 2025).

However, reliance on single biomarkers presents inherent limitations, as no individual parameter fully reflects the complexity of inflammation or consistently predicts clinical outcomes (Bettcher et al., 2025; Menzel et al., 2021). Consequently, recent reviews and clinical guidelines increasingly recommend multi-marker approaches that integrate inflammatory proteins, cytokines, and composite hematological indices to achieve more comprehensive and clinically meaningful inflammatory profiling (Fabris et al., 2022; Visser et al., 2022).

In light of these considerations, a structured and comprehensive overview of blood-based inflammatory biomarkers is warranted. This review aims to summarize the blood-based inflammatory biomarkers and to present a clear description of their characteristics, strengths, and limitations. In addition, key concepts related to the clinical application and interpretation of these biomarkers as indicators of inflammatory activity are discussed.

METHOD

This study was designed as a literature review using secondary data from scientific publications. Articles published within the last five years (2021-2026) were identified from PubMed and Google Scholar using search terms related to blood-based inflammatory biomarkers and inflammatory conditions. Inclusion criteria comprised peer-reviewed original research articles and review papers published in English reporting clear objectives, methodologies, and outcomes related to blood-derived inflammatory biomarkers and their clinical application. Exclusion criteria included articles not focused on blood-based biomarkers or that addressed only general inflammation without specific biomarker data, paywalled or otherwise inaccessible full texts, and articles with insufficient biomarker comparison data. The selected articles were evaluated by assessing titles, abstracts, and full texts to ensure scientific rigor. Information from the included studies was compiled and analyzed descriptively to compare common findings, identify differences, and synthesize key considerations across different categories of blood-based inflammatory biomarkers, resulting in an integrated overview to support their clinical interpretation.

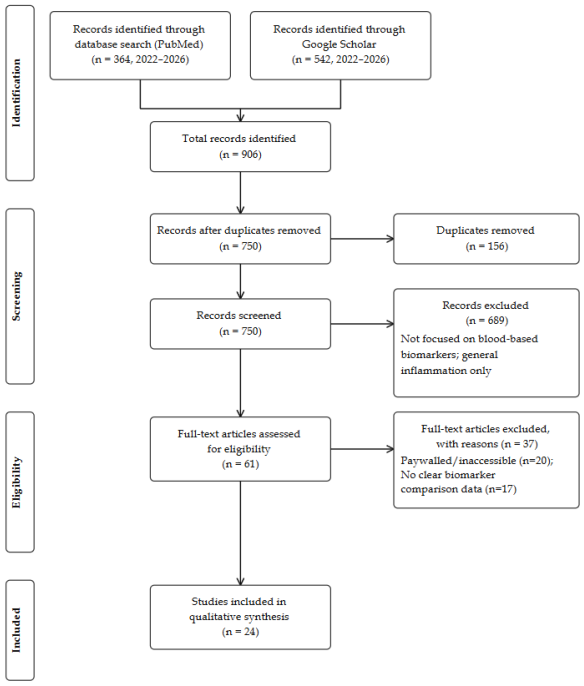

Figure 1. PRISMA Flow Diagram

RESULT

The results of this review are summarized in Table 1, which presents blood-based inflammatory biomarkers based on their biological characteristics and clinical relevance. The included biomarkers were classified into four major categories: acute-phase proteins; cytokines and chemokines; hematological markers and composite indices; and chronic inflammatory biomarkers. This classification reflects differences in inflammatory mechanisms, temporal dynamics, and applicability in clinical and research settings. The table integrates key information regarding biological roles, potential utility, and critical considerations for interpretation.

Table 1
Blood-Based Inflammatory Biomarkers, Biological Functions, and Considerations for Interpretation

Biomarker Class	Biomarker	Biological role in inflammation	Clinical / Research Utility	Key Notes for Interpretation	Citation
Acute-Phase Proteins	C-reactive protein (CRP)	Hepatic acute-phase reactant induced mainly by IL-6; reflects systemic inflammatory burden	Screening and longitudinal monitoring of systemic inflammation, infection, and cardio-metabolic risk	Highly sensitive but non-specific; influenced by age, obesity, and comorbidities	Liu et al., 2023; Rizo-tellez et al., 2023
	Serum amyloid A (SAA)	Acute-phase apolipoprotein rapidly upregulated during inflammation	Detection of acute and subclinical inflammation; autoimmune and infectious conditions	Often more sensitive than CRP in early or high-intensity inflammation	Chen et al., 2023; Pansini et al., 2025; Sorić Hosmanet al., 2021
	Fibrinogen	Acute-phase protein and coagulation factor linking inflammation and thrombosis	Risk stratification for cardio-vascular disease and thrombo-inflammatory states	Reflects interaction between inflammation and coagulation pathways	Hamidullah et al., 2025; Liu et al., 2023
	Ferritin	Iron storage protein functioning as an acute-phase reactant	Marker of hyper-inflammation, macrophage activation, and severe infection	Elevated in cytokine storm and chronic inflammatory disorders	Chen et al., 2023
	Procalcitonin (PCT)	Peptide precursor induced preferentially during bacterial infection	Differentia-tion of bacterial versus viral infection; antibiotic stewardship	Relatively specific for systemic bacterial infection and sepsis	Chen et al., 2023; Pournag et al., 2024
Cytokines and Chemokines	Interleukin-6 (IL-6)	Central pro-inflammatory cytokine linking innate and adaptive immunity	Disease activity and prognostic marker in autoimmune, cardio-vascular, and metabolic disorders	Strong clinical relevance but high biological variability	Iordache et al., 2025
	Tumor necrosis factor-α (TNF-α)	Master regulator of chronic inflammation and autoimmunity	Therapeutic target and biomarker in inflammatory and autoimmune diseases	Widely targeted by biologic therapies	Barichello et al., 2022; Murayama et al., 2023
	IL-1β / IL-17 / IL-23	Key drivers of Th17-mediated inflammatory pathways	Disease phenotyping and therapeutic stratification in autoimmune disorders	Represent pathway-specific inflammatory "signatures"	Liang & Xu, 2025; Murayama et al., 2023
Cytokines and Chemokines	IL-10 / TGF-β / IL-4	Anti-inflammatory and immunoregulatory cytokines	Assessment of immune regulation and resolution of inflammation	Typically interpreted as counter-regulatory responses	Liu et al., 2021

Biomarker Class	Biomarker	Biological role in inflammation	Clinical / Research Utility	Key Notes for Interpretation	Citation
	CXCL8	Neutrophil-recruiting and pro-angiogenic chemokines	Acute infection, cancer progression, and therapy resistance	Reflect neutrophil-driven inflammatory activity	Yin et al., 2024
	CXCL9, CXCL10, CXCL11, CXCL12	Regulators of T-cell trafficking and immune cell recruitment	Biomarkers of immune activation and response to immune-therapy	Context-dependent pro- or anti-tumor effects	Reschke et al., 2024; Wei et al., 2024
	CCL5, CCL20	Chemokines mediating T-cell, macrophage, and immune cell recruitment	Characteriza-tion of chronic inflammation and tumor micro-environment	Associated with immune cell infiltration and persistence	Long et al., 2025; Zheng et al., 2023
Hemato-logical Markers and Composite Indices	Neutrophil-to-lymphocyte ratio (NLR)	Reflects balance between innate and adaptive immune responses	Prognostic marker in infection, cancer, and cardio-vascular disease	Low-cost and accessible but non-specific	Buonacera et al., 2022; Islam et al., 2024; Wang et al., 2023
	Platelet-to-lymphocyte ratio (PLR)	Indicator of platelet activation and inflammatory stress	Marker of chronic inflammation and pro-thrombotic risk	Influenced by hemato-logical and systemic conditions	Islam et al., 2024; Wang et al., 2023; Yao et al., 2023
	Systemic immune-inflammation index (SII)	Composite index integrating neutrophils, platelets, and lymphocytes	Integrated assessment of systemic inflammatory burden	More compre-hensive than single-cell ratios	Choucair et al., 2023; Islam et al., 2024; Liu et al., 2025; Wang et al., 2023
Chronic Inflam-matory Biomarkers	GlycA / GlycB (NMR-based)	Composite signal of circulating acute-phase glycoproteins	Marker of chronic low-grade inflammation and cardio-metabolic risk	Stable and reproducible; requires specialized analytical platforms	Lodge et al., 2025
	Soluble urokinase plasmi-nogen activator receptor (suPAR)	Reflects sustained immune activation and chronic inflammation	Prognostic biomarker for disease severity and mortality risk	Relatively stable and less affected by acute inflam-matory fluctuation	Rasmussen et al., 2021

DISCUSSION

Acute Phase Proteins

Acute-phase proteins (APPs) are a class of blood-based biomarkers that exhibit marked concentration changes in response to inflammatory stimuli, infection, or tissue injury. These proteins are synthesized primarily in the liver, a process mediated by the activation of proinflammatory cytokines, most notably IL-6, IL-1β, and TNF-α (Fasulkov et al., 2022). Consequently, APPs serve as indicators of generalized inflammation rather than organ specific pathology (Jarlborg & Gabay, 2022).

C-reactive protein (CRP) is the most extensively utilized acute phase protein in clinical practice and research. Elevated CRP levels signify active inflammation and correlate directly with the magnitude of the inflammatory response (Pepys, 2021). Due to its high sensitivity and relatively short half life, CRP is a preferred tool for detecting acute episodes and performing serial monitoring of inflammatory status. However, CRP lacks specificity and can rise across a broad spectrum of conditions; thus, its interpretation requires careful clinical correlation (Libby, 2021).

Beyond CRP, several other APPs are clinically relevant, including serum amyloid A

(SAA), fibrinogen, ferritin, haptoglobin, and procalcitonin (Hartigh et al., 2023; Kumar et al., 2025; Menzel et al., 2021). SAA demonstrates a rapid escalation, potentially increasing up to 1000-fold, often providing a more sensitive indicator of early or high-intensity acute inflammation than CRP (Hartigh et al., 2023; Sorić Hosman et al., 2021). In contrast, fibrinogen and ferritin are typically associated with persistent inflammation and are frequently elevated in low-grade chronic states, such as metabolic disorders or post-acute sequelae of COVID-19 (Laudisio et al., 2023; Maamar et al., 2022).

Procalcitonin serves as a more selective marker for bacterial infections and sepsis, aiding in systemic evaluation and informing clinical decisions on antibiotic stewardship (Chambliss et al., 2023; Schuetz, 2022). Recent analytical advances have also introduced NMR-based biomarkers, such as GlycA and GlycB. These markers represent composite signals of multiple glycoproteins and offer a stable, consistent measure of the overall systemic inflammatory burden (Lodge et al., 2025).

The primary advantage of APPs as blood-based biomarkers is their widespread availability in routine clinical panels (Prabhala et al., 2021). Their measurement protocols are highly standardized, facilitating seamless integration into both clinical workflows and research studies (Mallagaray et al., 2023). Furthermore, most APPs exhibit robust analytical stability and can be quantified using standard immunological assays (Engelmaier et al., 2025).

Despite these strengths, the clinical utility of APPs is limited by low biological specificity, as elevations occur in response to various etiologies of tissue damage (Powanda & Moyer, 2021). Therefore, they are best utilized as general indicators of disease activity and for monitoring therapeutic efficacy (Kumar et al., 2025; Raju et al., 2025). To enhance diagnostic and prognostic precision, the interpretation of APPs should be combined with other biomarkers, such as specific cytokines or markers of direct tissue injury (Gautreaux et al., 2022).

Cytokines and Chemokines

Cytokines and chemokines are inflammatory signaling molecules that facilitate intercellular communication during an immune response (Damme et al., 2025). These proteins are synthesized by immune and various tissue cells upon exposure to stimuli, playing critical roles in the initiation, amplification, and regulation of the inflammatory cascade (Megha et al., 2021).

In contrast to acute-phase proteins that reflect downstream systemic effects, cytokines and chemokines characterize inflammatory regulatory activity at an earlier phase (Damme et al., 2025). Pro-inflammatory cytokines, specifically IL-1β, IL-6 TNF, are established indicators of inflammatory status (Yameny, 2025). IL-1β and TNF are involved in the primary stages of inflammation by inducing endothelial activation and secondary mediator production (Garlanda et al., 2025). Furthermore, IL-6 acts as a central mediator linking innate and adaptive immunity while stimulating hepatic synthesis of acute-phase proteins (Al-qahtani et al., 2024). Consequently, circulating cytokine levels frequently correlate with other inflammatory markers such as C-reactive protein (CRP) (Megha et al., 2021).

In addition to pro-inflammatory mediators, anti-inflammatory cytokines like IL-10 serve as significant biomarkers by reflecting the regulatory and compensatory mechanisms against ongoing inflammation (Carlini et al., 2023; Ehlting et al., 2021). Ratio of pro-inflammatory to anti-inflammatory cytokines is often utilized to assess immunological balance, particularly in cases of severe or persistent systemic inflammation (Hadžimusić & Hadžijunuzović-Alagić, 2025).

Chemokines are a functional subset of cytokines that direct the recruitment and migration of immune cells to inflammatory loci (Damme et al., 2025). Specific molecules, including CCL2 and CXCL10, indicate the activation and recruitment of circulating monocytes and lymphocytes (Speeckaert et al., 2023). As biomarkers, chemokines provide quantitative data on immune cell trafficking dynamics rather than solely indicating inflammatory intensity (Iordache et al., 2025).

The quantification of these biomarkers in blood is typically performed using immunological assays, such as Enzyme-Linked Immunosorbent Assay (ELISA). The clinical relevance of these markers is high due to their specificity to distinct inflammatory pathways (Moreno-guerrero et al., 2025). However, limitations include low systemic concentrations, short half-lives, significant biological variability, and the requirement for high-sensitivity analytical techniques (Radonjic-Hoesli et al., 2022).

Hematological Markers and Composite Indices

Hematological markers are blood-based inflammatory indicators derived from routine

complete blood count (CBC) analyses (Wei et al., 2022). These parameters reflect alterations in the distribution and proportion of immune cell subsets during the inflammatory process. Systematic changes in the counts of neutrophils, lymphocytes, monocytes, and platelets form the foundation for developing composite inflammatory indices, which are widely accessible in both clinical practice and research (Islam et al., 2024).

The most frequently utilized composite indices include the neutrophil-to-lymphocyte ratio (NLR), the platelet-to-lymphocyte ratio (PLR), and the systemic immune-inflammation index (SII) (Islam et al., 2024). These indices characterize the homeostatic balance between effector immune cells (e.g., neutrophils and monocytes) and the adaptive immune compartment (lymphocytes). An elevation in these ratios typically signifies active systemic inflammation (Kourilovitch & Maldonado, 2022).

As biomarkers, hematological indices function as surrogate markers of inflammation (Cosma et al., 2025). While they do not delineate specific molecular pathways, they offer a concise overview of the overall inflammatory status. Because they are calculated from routine laboratory parameters, these composite indices are frequently employed for longitudinal monitoring and the stratification of inflammatory severity across diverse clinical conditions (Islam et al., 2024).

The primary advantages of hematological markers and their composite counterparts are their widespread availability and seamless integration into daily clinical workflows (Y. Wei et al., 2022). These assessments can be performed repeatedly without requiring supplementary procedures, making them highly suitable for large-scale population studies (Cosma et al., 2025). Consequently, hematological indices serve as pragmatic and applicable tools for inflammatory assessment (Islam et al., 2024).

However, the clinical utility of these markers is constrained by low biological specificity (Islam et al., 2024). Index values can be confounded by non-inflammatory factors, including physiological stress, hydration status, hemorrhage, pharmacological interventions, and underlying hematological disorders (Walzik et al., 2021). Therefore, hematological indices should be interpreted in conjunction with other specific biomarkers to enhance diagnostic and prognostic accuracy (Islam et al., 2024).

Blood-Based Chronic Inflammatory Biomarkers

Low-grade chronic inflammation is a persistent inflammatory state that typically remains clinically asymptomatic, yet serves as a critical driver in the progression of various chronic diseases. Assessing this condition necessitates the use of blood-based biomarkers that demonstrate relative stability and accurately reflect long-term inflammatory activity (Rasmussen et al., 2021).

Conventionally, elevated levels of acute-phase proteins, such as C-reactive protein (CRP), have been utilized as indicators of chronic inflammation. These biomarkers reflect continuous inflammatory activation, although they lack specificity regarding the localized source of the inflammation (Raju et al., 2025).

Recent advancements in analytical technologies have introduced more reliable chronic inflammatory markers, most notably GlycA and GlycB, which are derived from Nuclear Magnetic Resonance (NMR) spectroscopy (Fung et al., 2023; Lodge et al., 2025). These biomarkers represent the integrated signal of multiple circulating acute-phase glycoproteins and are notably less susceptible to the acute fluctuations characteristic of transient inflammatory spikes (Mallagaray et al., 2023). Consequently, GlycA and GlycB are increasingly regarded as more consistent indicators of systemic chronic inflammation (Lodge et al., 2025).

Beyond glycoprotein-based markers, soluble urokinase plasminogen activator receptor (suPAR) has emerged as a blood-based biomarker that reflects chronic inflammation through sustained immune activation rather than transient acute-phase responses (Rasmussen et al., 2021). suPAR represents the circulating form of the membrane-bound urokinase plasminogen activator receptor (uPAR) released from activated immune cells, including neutrophils and monocytes, linking its plasma concentration to persistent inflammatory and immune activation processes (Belvederi et al., 2025). Unlike acute-phase inflammatory markers, circulating suPAR levels demonstrate high temporal stability and are minimally influenced by short-term inflammatory stimuli, making suPAR particularly suitable for the assessment of low-grade chronic inflammation (Rasmussen et al., 2021; Vasbinder et al., 2024). Elevated suPAR concentrations have been consistently associated with disease severity, progression, and adverse outcomes across a wide range of chronic conditions, supporting its role as a robust indicator

of long-term inflammatory burden (Belvederi et al., 2025; Rasmussen et al., 2021).

Despite the availability of several stable chronic inflammatory biomarkers, chronic inflammation reflects a biologically complex and multidimensional process. No single biomarker fully captures its heterogeneity. For this reason, multi-biomarker approaches have gained increasing prominence. By combining acute-phase proteins, cytokines, chemokines, and hematological parameters, these strategies enable a more comprehensive characterization of persistent inflammatory states and immune regulation (Menzel et al., 2021; Raju et al., 2025).

Although chronic inflammatory biomarkers provide valuable insights into long-term systemic inflammation, their implementation in clinical settings remains limited. Major challenges include the need for specialized analytical platforms, higher operational costs, and the current lack of globally standardized clinical thresholds (Rasmussen et al., 2021).

Challenges and Future Directions in the Interpretation of Blood Based Inflammatory Biomarkers

Blood based inflammatory biomarkers play a critical role as indicators of inflammation (Pritzker, 2023). However, the interpretation of these markers involves several challenges that must be addressed to avoid erroneous clinical conclusions (Bettcher et al., 2025). A primary obstacle is the inherently non-specific nature of most circulating inflammatory indicators. While elevations in acute phase proteins, cytokines, and hematological parameters signify inflammatory activation, they do not provide definitive information regarding the specific source, underlying cause, or anatomical location of the inflammation (Germolec et al., 2018). Consequently, blood biomarkers should not be utilized as standalone diagnostic tools and must be interpreted within a broader biological and clinical framework (Bettcher et al., 2025).

Biological variability further complicates the interpretation of inflammatory markers. Factors such as age, biological sex, nutritional status, comorbidities, and metabolic disturbances can significantly influence systemic biomarker levels (Inamdar et al., 2025). Additionally, differences in analytical methodologies, preanalytical conditions, and the timing of sample collection contribute to measurement variations. These discrepancies limit the comparability across different studies and hinder the application of uniform clinical thresholds (O'Donnell et al., 2025).

Another significant challenge is the limited sensitivity and stability of certain biomarkers, particularly cytokines and chemokines that circulate at very low concentrations. Rapid fluctuations and the requirement for high-sensitivity analytical methods make these markers difficult to implement in routine clinical practice (Jiers et al., 2025). Conversely, more stable biomarkers often lack biological specificity, leading to a trade off between analytical stability and biological precision (Pritzker, 2023).

To overcome these limitations, the multi biomarker approach is gaining increased attention. Combining acute phase proteins, cytokines, and hematological indices allows for a multidimensional assessment of inflammation, which can improve both diagnostic and prognostic accuracy (Bruserud et al., 2020). Future advancements in this field should focus on the standardization of analytical techniques, the optimization of sample handling prior to testing, and the validation of more precise clinical threshold values (Callaghan & Roth, 2020). Furthermore, the integration of omics technologies, multiplex proteomic panels, and large scale data analysis driven by artificial intelligence is expected to generate individual inflammatory profiles that are more consistent and clinically applicable (Pritzker, 2023). Through these integrated approaches, blood based inflammatory biomarkers have the potential to be more effectively incorporated into broad clinical practice (Raju et al., 2025).

CONCLUSION

This review summarizes major blood-based inflammatory biomarkers and describes their characteristics, strengths, and limitations as indicators of inflammatory activity. Acute-phase proteins reflect the systemic inflammatory burden; cytokines and chemokines indicate immune signaling pathways; hematological indices represent inflammatory stress; and chronic inflammatory biomarkers capture sustained immune activation associated with long-term disease risk. Each biomarker group reflects a distinct aspect of inflammation, and none alone comprehensively represents inflammatory processes. Interpretation that integrates multiple biomarker classes supports clearer clinical application and more accurate evaluation of inflammatory status.

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