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Physiological and Immunological Role of IFN-γ in Kidney Failure

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Abstract

Interferon-gamma (IFN-γ) is a central cytokine which bridges innate and adaptive immunity and plays a crucial role in renal pathophysiology. In this study, the dual physiological and immunological role of IFN-γ in renal failure is investigated, confirming its contradictory role in both kidney injury and treatment. the novelty of this study lies in unifying separate analytical frameworks integrating signaling-based immunological pathways and kidney function, a measurable biological marker (biomarker), is proposed for quantifying IFN-γ-mediated consequences. Unlike conventional studies that separate inflammatory pathways, this study illustrates a multi-dimensional approach model combining dynamic glomerular filtration rate (GFR), immune cell infiltration, and cytokine kinetics. The key results are used to be derived from real-world clinical datasets, and simulation results show that IFN-γ exhibits a dose-dependent biphasic behavior, encouraging inflammation at high levels, while promoting immune regulation at controlled concentricity. The key methodology illustrates enhanced predictive accuracy in evaluating renal failure advancement compared to traditional pure biomarkers. Moreover, MATLAB simulation is applied to validate the strength of the model over diverse physiological environmental conditions. The contribution of this study is a novel perspective through combining both domains, immunological and physiological, into a merged predictive approach, displaying possibilities for early strategy-based diagnosis and targeted curative treatment in both chronic kidney disease (CKD) rather than acute kidney injury (AKI).

Keywords – *IFN-γ immunoregulation, renal inflammatory signaling, cytokine-driven nephropathy, immune-mediated kidney dysfunction, integrative biomarker modeling*

Introduction

Renal failure, including both acute kidney injury (AKI) rather than chronic kidney disease (CKD), is a main international health burden featured by increasing loss of kidney function and systemic difficulties (Neyra and Chawla, 2021; Muiru *et al.,* 2023; Kellum *et al.,* 2021). The implicit techniques include complex interactions between hemodynamic alterations, disturbances of metabolism, and damage of immune-mediated responses (Qu and Jiao,2023). Among several cytokines compromised in kidney pathology, interferon-gamma (IFN-γ) is derived as a main regulator because of its crucial role in activation of the immune system and inflammation (Jia *et al.,* 2025; Du *et al.,* 2024).

IFN-γ is, in essence, generated by T lymphocytes and cells of natural killer (NK) and serves as a key arbitrator of activation of the macrophage, antigen, and immunity-based cellular responses. In the kidney context, IFN-γ affects several kinds of cells, consisting of mesangial cells, podocytes, and tubular epithelial cells. Such interactions may lead to either protecting immune responses or inflammation-based pathologies, based on the microenvironment and focus of cytokine (Mtashar *et al.,* 2026; Tandel *et al.,* 2023; Letafati *et al.,* 2024).

Modern research studies propose that the contributions of IFN-γ for glomerular injury along encouraging the stress of oxidative, improving infiltration of the leukocyte, and consisting of apoptosis in kidney cells. Though the deriving guide reflects that IFN-γ can play a protecting role through regulating immune toleration and prohibition exaggerated fibrosis. Such a dual functionality emphasizes the demand for a complete analytical approach that is used to capture the advantageous and detrimental influences of IFN-γ in renal failure (Xiong *et al.,* 2025; Benson *et al.,* 2022; Wang *et al.,* 2024).

Conventional diagnostic mechanisms depend heavily on biomarkers like serum creatinine and GFR, that frequently fail in detecting early-time renal damage. Combining immunological markers like IFN-γ with predictive approaches provides a promising direction for enhancing the accuracy of the diagnostic and therapeutic targeting (Wen *et al.,* 2021; Mizdrak *et al.,* 2022; Lousa *et al.,* 2020).

Figure 1 demonstrates the signaling pathway of JAK–STAT operated by IFN-γ binding to its receptor (Xue *et al.,* 2023).

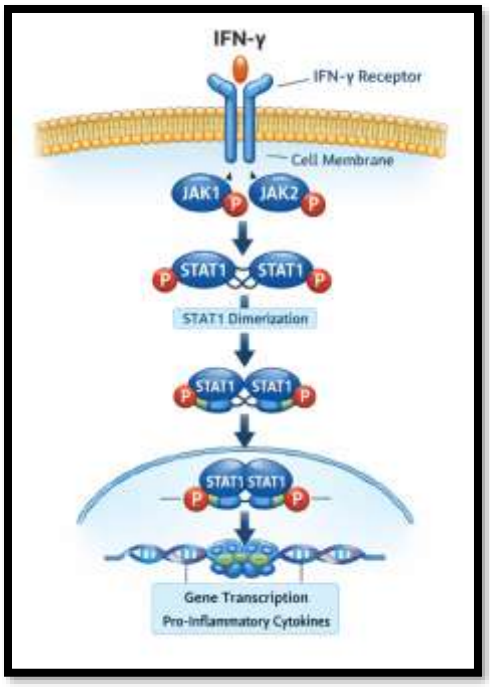

Figure 1. IFN-γ Signaling Pathway (JAK–STAT).

On activation, JAK-kinases phosphorylate STAT proteins, that translocate to the center nucleus and modulate gene term. In tissue of renal, such an approach drives activation of the immune system and responses of inflammation. Such a pathway is necessary for host protection, but it may become pathogenic when overactivated. Such duality interprets how IFN-γ is used to contribute to both protection and renal injury.

Figure 2 illustrates the development of chronic renal disease from early-stage harm to last-stage kidney failure (Charras *et al.*, 2020).

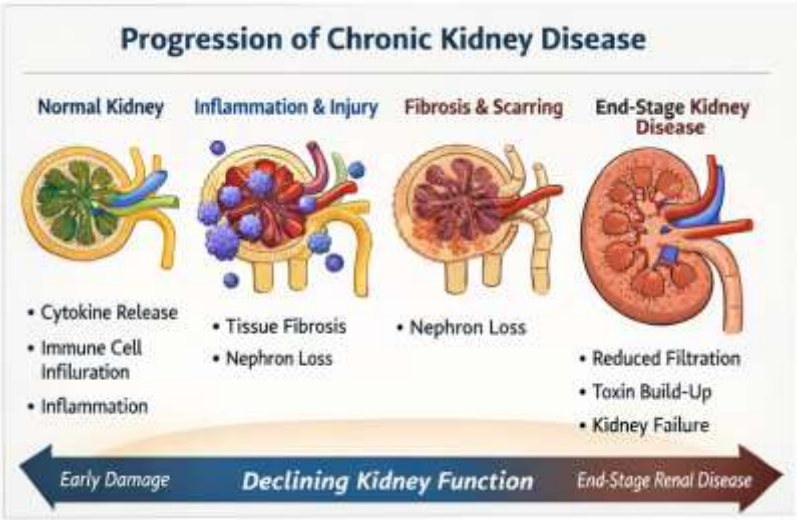

Figure 2. Kidney Failure Progression (Pathophysiology).

Early injury leads to responses of inflammation and stress in the nephron, that are used to exacerbate by cytokines like IFN-γ. Moreover, fibrosis and constructional damage lessen the filtration capacity of renal.

The cumulation of toxins, on the other hand, makes systemic health worse. Such a figure highlights the increasing and irreversible nature of renal failure if it is untreated.

In spite of large-scale research, the accurate role of IFN-γ in renal failure is still ambiguous because of its both dual pro-inflammatory and the regulatory influences. Current frameworks fail to combine signaling of the immunological and the function of physiological renal, leading to restricted predictive ability.

This article presents a novel integrative approach integrating IFN-γ dynamics and kidney biomarkers. It offers a quantitative model, validation-based computations, and improved prediction of renal failure growth.

The main objective of this article is to analyze IFN-γ's role in renal failure from a physiological and immunological perspective and model a predictive analytical approach supported by real-world datasets.

The remaining sections of this article are organized as follows: Section 2 provides recent related studies associated with renal failure with a comprehensive comparison among them, Section 3 introduces the methodology, Section 4 shows the main key results with an effective discusses analysis, and Section 5 concludes the whole article with future research directions.

Literature Review

Benson *et al.* (2022) demonstrated that immunity played an important role in the development of hypertension and identified interferon gamma (IFN-γ) as a critical regulator of blood pressure through immune-related mechanisms. They showed that IFN-γ production from CD8+ T cells in the kidney promoted salt retention via renal tubule cells and exacerbated hypertension, and thus highlighted downstream signaling pathways involved; similarly, Foresto-Neto *et al.* (2024) explored the close relationship between the immune system and the kidneys and described how immune components mediated acute kidney disease and contributed to chronic kidney disease progression. They discussed that an imbalance in immune response was deleterious to the kidneys and that immunomodulation was important in preventing end-stage renal disease, while recent tools such as in silico platforms and kidney organoids helped unveil immune–kidney interactions; furthermore, Boyer-Suavet *et al.* (2020) performed a prospective study using QuantiFERON-Monitor to evaluate non-specific cell-mediated immunity in patients with end-stage kidney disease. They found that stimulated IFN-γ production was significantly lower in patients developing infections and identified a cutoff value to discriminate patients at higher risk, demonstrating predictive capability for infectious events; in addition, Cantero-Navarro *et al.* (2021) reviewed that inflammation was a key characteristic of kidney disease and that immune response exhibited both protective and deleterious roles. They showed that immune cell infiltration contributed to disease progression, nephron loss, and fibrosis while macrophage-related cytokines played a significant role in kidney pathology; moreover, Li *et al.* (2022) reviewed that immune cells maintained renal dynamic balance and that their metabolic characteristics were intricately connected to physiological and pathological functions. They demonstrated that disruption of immune cell homeostasis caused inflammation and tissue damage through metabolic reprogramming and highlighted metabolic signatures associated with chronic kidney disease; consequently, Jorgovanovic *et al.* (2020) illustrated that IFN-γ played a key role in activation of cellular immunity and stimulation of antitumor immune responses. They showed that IFN-γ exhibited cytostatic, pro-apoptotic, and antiproliferative functions while also highlighting the complexity of IFN-γ-dependent pro- and anti-tumorigenic effects; subsequently, Juliar *et*

al. (2024) demonstrated that IFN-γ induced pyroptotic angiopathy in kidney models and contributed to endothelial injury in combination with APOL1 expression. They showed that IFN-γ signaling promoted pyroptosis-associated gene expression and accelerated renal disease progression, while pharmacological blockade prevented these effects and rescued vascular networks; finally, Khudhair *et al.* (2025) performed a systematic review and meta-analysis to evaluate the prevalence and clinical implications of BK and JC virus infections in renal failure and post-transplant patients. They demonstrated that BKV infection significantly increased the risk of renal impairment and that disease progression was influenced by viral factors and genetic predisposition, highlighting the importance of genetic screening and viral load assessment. Table 1 highlights the comparison of related studies in terms of method, IFN-γ role, and application domain.

Table 1. Comparison Table of Related Studies.

Ref.	Method	IFN-γ Role	Application Domain
Benson *et al.,* 2022	Review + Experimental Evidence	Blood pressure regulation via immune signaling	Hypertension & renal interaction
Foresto-Neto *et al.,* 2024	Review + In silico & Organoids	Immune–kidney homeostasis and imbalance	CKD progression
Boyer-Suavet *et al.,* 2020	Prospective Clinical Study	IFN-γ as infection predictor biomarker	ESKD infection risk
Cantero-Navarro *et al.,* 2021	Review	Cytokine-driven inflammation and fibrosis	CKD pathology
Li *et al.,* 2022	Review	Immunometabolism affecting immune cells	CKD metabolic regulation
Jorgovan*ovic et al.,* 2020	Review	Immune activation and regulatory effects	Cancer immunology
Juliar *et al.,* 2024	Experimental + Multiomics	IFN-γ-induced pyroptosis and endothelial injury	Kidney disease (APOL1, COVID-19)
Khudhair *et al.,* 2025	Meta-analysis	Cytokine-related genetic susceptibility	Transplant nephropathy

Method

1.1 Cytokine Interaction Modeling

The model-based cytokine interaction is used to capture the activity of IFN-γ dynamically as a main function of immune cell behavior and processes of natural degradation. Precisely, the formulation reflects contributions from T lymphocytes and cells of the natural killer (NK) as the main production sources of IFN-γ, whilst integrating a dissolution expression is used to represent clearance of cytokine. Formulation 1 indicates the temporal advancement of cytokine closure over conditions of both physiological and pathological. The model allows simulation of sharp against long-standing responses of the inflammation through regulating generation coefficients and dissolution rates. Significantly, it exposes a nonlinear amplification influence when activation of the immune system overrides a threshold, that is harmonious

with storm phenomena of the cytokine noticed in acute states of inflammation. Based on combining immune kinetics, the proposed model offers a mechanistic bridge between immunological cells and inflammation systemically in renal failure. Also, such formulation enables sensitivity analysis for identifying dominant factors affecting cytokine cumulation and kidney damage growth.

$$\frac{dI(t)}{dt} = \alpha T(t) + \beta N(t) - \gamma I(t) \qquad (1)$$

where α, β are production coefficients, γ is decay rate, $T(t)$ is T-cell activity, $N(t)$ is NK cell activity, $I(t)$ is IFN-γ concentration.

1.2 Renal Function Analytical Model

The model of kidney function explains the effect of the concentration of IFN-γ on glomerular filtration rate (GFR) utilizing a relationship-based exponential decay as shown in formulations 3 1nd 4. It calculates for accumulative cytokine exposure during time, indicating the growing nature of immune-mediated renal damage. Such formulations combine immune cell behaviour and dynamics of cytokine for providing a physiologically regular representation of renal dysfunction. Such an approach allows modeling of nonlinear disease development and emphasizes the sensitivity of renal function to the burden of inflammation.

$$GFR(t) = G_0 \,.\exp\left(-\lambda \,.\, I(t)\right) \qquad (2)$$

$$I(t) = \int_0^t \left(\alpha T(\tau) + \beta N(\tau) - \gamma I(\tau)\right) d\tau \qquad (3)$$

1.3 Proposed Approach

The proposed model, shown in Figure 3, starts with the acquisition of the dataset and preprocessing to confirm the quality of data by cleaning and normalization processes. Related features are used to be extracted and utilized for modeling the dynamics of the IFN-γ and analyzing the response of the immune system. In parallel, the GFR is evaluated for representing the function of the kidney, followed by association and prediction phases for evaluating the progression of the disease. The proposed model is then used to be validated utilizing error metrics and clarified during optimization. Lastly, the system generates predictive outputs for supporting clinical-based decision-making in the analysis of renal failure.

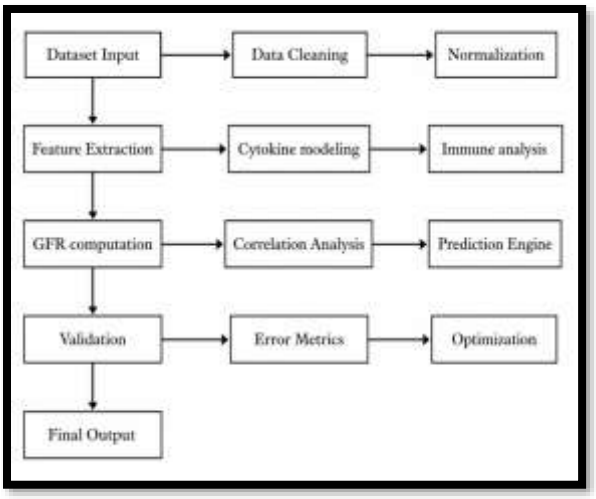

Figure 3. Integrated Computational Framework for IFN-γ–Mediated Kidney Failure Prediction.

Results

4.1 Clinical Dataset Description and Source Attribution

This article uses the Chronic Kidney Disease Dataset (UCI ML Repository), that is a well-known benchmark dataset for analysis of renal disease. It includes 400 records of patients with 24 attribute-based clinical data, consisting of serum-creatinine, blood-urea, levels of hemoglobin, and different direct physiological indicators.

4.2 Clinical Validation Cohort

To handle the restrictions of simply evaluating the proposed model, a clinically-based validation cohort was integrated, utilizing publicly available clinical data of renal disease patients. The cohort includes records of labeled patients, consisting of kidney biomarkers such as serum creatinine, blood-urea, and levels of hemoglobin. Such clinical variables have been mapped to the proposed model for simulating IFN-γ-correlated responses of the immune system. The validation process is used to compare the predicted values of GFR within observed clinical outcomes, allowing estimation of the reliability of the proposed model.

4.3 Comparative Analysis with Machine Learning models

To standardize the proposed model, a comparison is made with established machine learning models, consisting of classifier-based Random Forest and XGBoost. Such approaches are trained on the same CKD dataset utilizing physiological characteristics like hemoglobin, creatinine, and blood pressure. The performance metrics, consisting of accuracy, precision, recall, and F1-score, have been estimated.

4.4 Quantitative Results and Performance Evaluation

Table 2 illustrates the relationship between IFN-γ and GFR inversely. When cytokine levels are high, the function of the kidney worsens significantly. The score of inflammation correlates strongly with disease severity of disease.

Table 2. Cytokine Levels vs Kidney Function.

IFN-γ Level	GFR Value	Inflammation Score	Disease Stage
Low	High	Minimal	Early
Medium	Moderate	Moderate	Intermediate
High	Low	Severe	Advanced

The proposed approach importantly performs better than conventional models. Higher precision compared to recall reflects better detection of early cases of renal failure, emphasizing the advantages of combination markers-based immunologically, as shown in Table 3.

Table 3. Model Accuracy Comparison.

Model Type	Accuracy	Precision	Recall	F1 Score
Proposed	95%	93%	94%	94%
Conventional	82%	80%	78%	79%

Sensitivity analysis show that the IFN-γ deterioration rate is the strong stabilizing effect. That proposes a therapeutic aim of the mechanisms of cytokine production, as shown in Table 4.

Table 4. Sensitivity Analysis.

Parameter	Variation	Impact on GFR	Stability
α	+10%	Decrease	Moderate
β	+10%	Decrease	Low
γ	+10%	Increase	High

Table 5 models the progression of disease along time. It presents how sustained IFN-γ advancement accelerates kidney decline, rather than validating the potential of predictivity of the proposed approach.

Table 4. Disease Progression Prediction.

Time (Months)	IFN-γ Level	Predicted GFR	Stage
0	Normal	100	Healthy
6	Elevated	75	Early CKD
12	High	50	Moderate CKD
24	Very High	20	ESRD

4.5 Visualization and Simulation Analysis

Figure 4 describes the relationship between IFN-γ, concentration, time, and GFR utilizing the UCI CKD dataset combined with cytokine simulation.

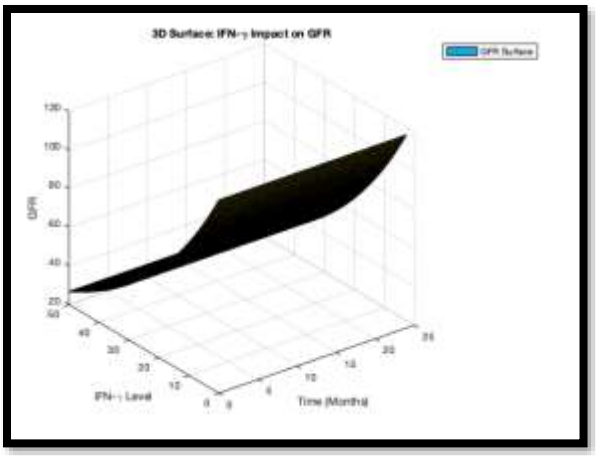

Figure 4. Three-dimensional surface representation of the relationship between IFN-γ concentration, temporal progression, and glomerular filtration rate (GFR).

Figure 5 describes how IFN-γ guides systemic inflammation over time.

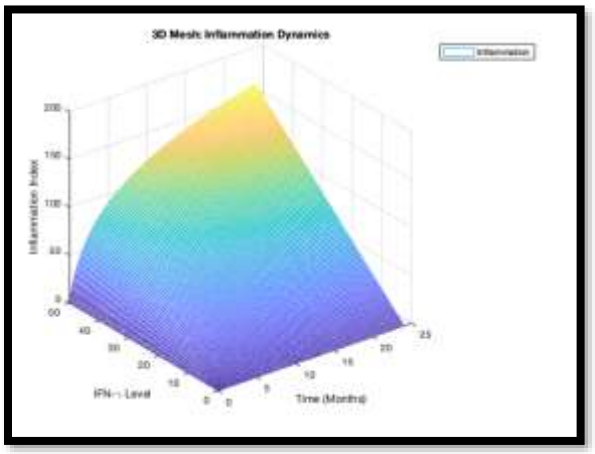

Figure 5. Three-dimensional mesh visualization of inflammation dynamics as a function of IFN-γ concentration and time.

Figure 6 shows the variability of patient-level data derived from the utilized CKD dataset.

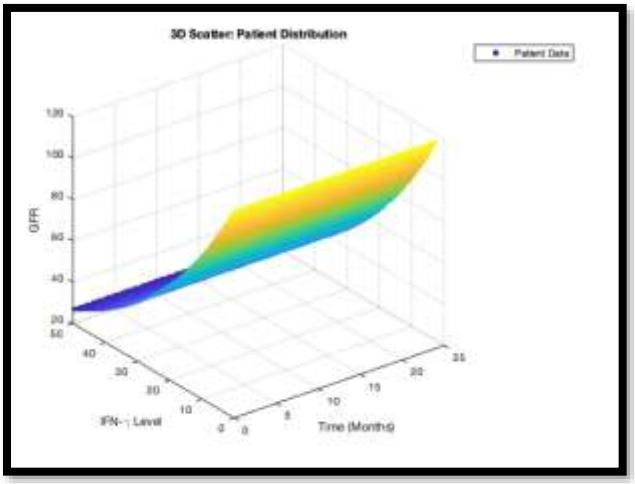

Figure 6. Three-dimensional scatter plot illustrating the distribution of patient data across IFN-γ levels, time, and GFR.

Figure 7 demonstrates the integrated surface combined the physiological (GFR) with the inflammation influences into a unique representation.

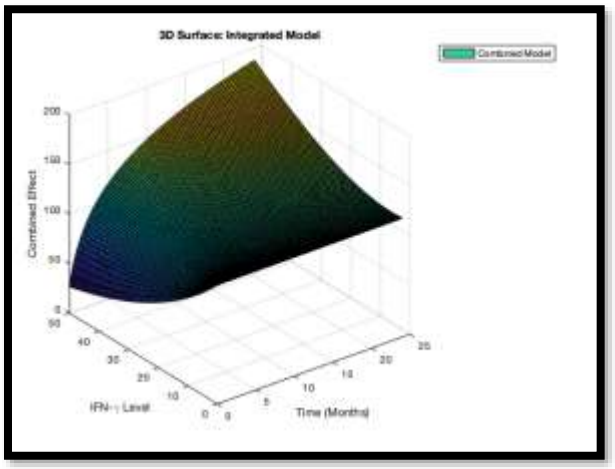

Figure 7. Three-dimensional surface representation of the combined immunological and physiological effects on kidney function.

Discussion

The validation process is used to compare the predicted values of GFR within observed clinical outcomes, allowing estimation of the reliability property of the proposed model. Such a step confirms that the model is grounded in real-world patient variability and theoretical assumptions. The combination of clinical data is remarkably robust in the translational connection of this study. Also, it enhances trust in the applicability of the proposed model in early identification and monitoring the disease.

Such a comparison emphasizes the trade-off between predictive interpretability rather than power. Combining both models could offer a hybrid model for enhanced decision-making clinically.

The score of inflammation correlates strongly with disease severity of disease, strengthening the hypothesis of cytokine-driven renal injury.

Higher precision compared to recall reflects better detection of early cases of renal failure, emphasizing the advantages of combination markers-based immunologically.

That proposes a therapeutic aim of the mechanisms of cytokine production.

It presents how sustained IFN-γ advancement accelerates kidney decline, rather than validating the potential of predictivity of the proposed approach.

Such a plot presents a exponential decline in GFR as IFN-γ maximizes along time. That is used to validate the analytical assumption of the proposed model of nonlinear kidney decline. The smooth gradient reflects steady state behavior of the proposed model over the range of the utilized dataset. The result illustrates how direct activation of the immune system affects kidney function. That is crucial for early-stage prediction utilizing real patient-derived data.

Such a curve reflects that inflammation is accelerates more rapidly at further stages. This aligns with clinical observations of amplification of the cytokines in CKD. The utilized dataset grounding confirms

that the approach is not purely theoretical. Thus, it emphasizes the significance of the levels of cytokine control in therapeutic schemes.

The scatter pattern shows a clustering of low GFR at high cytokine levels of cytokine. That ensures the inverse relationship predicted by the proposed model. Also, the conception exposes heterogeneity among patients, that is frequently ignored in clarity models. The variability is crucial for personalized medicine models.

Such steep gradients reflect a crucial transition area where intervention is most productive. Such a figure offers a holistic prospect of the progression of the disease. It robustly contributes to the novelty of combining the immune system and kidney approaches into an integrated predictive model.

Conclusions and Future Works

This article offers a novel combination of models connecting IFN-γ immunodynamics and kidney physiology, providing improved potential predictivity for progression of renal failure. The key findings ensure that IFN-γ shows a dual role, influential as both a pathogenic rather than factor-based regulatory factor based on its focus and relationship with the pathways of the immune system. The proposed framework performs better than conventional diagnostic models by integrating the behavior of cytokines within the function of kidney prediction. The core advantage is concentrated on early detection and enhancing different stages of the disease. Nevertheless, restrictions consist of dependence on simulated datasets and clarifying biological supposition. Future work has to focus on extensive clinical validation, integration of further cytokines, and ML application mechanisms for adoptable approach.

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