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Research Article

Evaluation of Interleukin-17A and Interleukin- 34 in Patients with Diabetic Foot Ulcer

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Abstract

Background: Diabetic foot ulcers (DFU) are chronic complications of diabetes, characterized by poor wound healing, persistent inflammation, and increased risk of infection or amputation. Interleukin-17A (IL-17A) is a pro-inflammatory cytokine produced mainly by T helper 17 (Th17) cells. It helps fight bacteria and fungi, while Interleukin-34 (IL-34) modulates monocytes and macrophages through binding to the CSF-1 receptor. Both cytokines are associated with chronic inflammatory and autoimmune conditions. This study aimed to evaluate and compare the diagnostic value of IL-17A and IL-34 in DFU patients.

Methods: A case-control study included 50 diabetic foot ulcer patients and 50 healthy people as a control group. Blood samples were collected for laboratory tests and to evaluate IL-17A and IL-34 serum levels in patients and controls using an enzyme-linked immunosorbent assay (ELISA) test.

Results: Serum IL-17A and IL-34 levels were significantly higher in DFU patients compared to controls (P = 0.000 and 0.044, respectively). IL-34 showed better diagnostic performance with an area under the curve (AUC) of 0.743, sensitivity of 0.78, and specificity of 0.64 (P = 0.000). IL-17A demonstrated an AUC of 0.638, with lower sensitivity (0.32) and higher specificity (0.96) (P = 0.017).

Conclusions: Both IL-17A and IL-34 levels were elevated in DFU patients. However, IL-34 demonstrated higher sensitivity and overall diagnostic accuracy, suggesting it may serve as a more reliable biomarker for early detection and diagnosis of diabetic foot ulcers.

Keywords: Diabetic foot ulcer, IL-17A, IL-34, ELISA

Introduction

Diabetes mellitus (DM) is a chronic condition marked by high blood sugar, leading to damage in organs like the eyes, kidneys, nerves, heart, and blood vessels [1], and may cause blindness, stroke, or amputations. Diabetic foot ulcers (DFUs) are a serious diabetes complication, caused by multiple factors [2]. Such as bacterial infection of damaged skin layers, and may require amputation to prevent further infection [3]. The main risk factors for DFUs are peripheral neuropathy and peripheral vascular disease, with trauma also playing a role in ulceration [4]. DFUs affect about 6.4% of diabetic patients, and the 5-year mortality risk is 2.5 times higher than in those without ulcers. The Infectious Disease Society of America (IDSA) and International Working Group on the Diabetic Foot (IWGDF) classify DFU infections as uninfected, mild, moderate, or severe based on clinical symptoms [5]. In diabetic wounds, poor blood supply, low oxygen levels, and high glucose delay healing and increase complications [2]. In diabetic patients, immune system dysfunction impairs infection control and delays wound healing, contributing to the worsening of diabetic foot ulcers (DFUs).

Interleukin-17A (IL-17A) belongs to the IL-17 cytokine family (IL-17A to IL-17F), with IL-17A and IL-17F being the main isoforms. These cytokines are strong pro-inflammatory mediators mainly secreted by Th17 cells, but also produced by natural killer (NK) cells, macrophages, neutrophils, dendritic cells, and mast cells [6]. IL-17A is involved in infection defense and autoimmune diseases like systemic lupus erythematosus, multiple sclerosis, asthma, and type 1 diabetes, and it activates JAK1,

JAK2, PI3K, and NF-κB pathways, promoting inflammation. High IL-17A levels in type 2 diabetes (T2D) suggest a role in its complications by triggering free radical production [7]. It helps in healing after injury, but prolonged activity can cause harmful tissue changes, leading to dysfunction [8]. Interleukin-34 (IL-34), identified in 2008 as a ligand for colony-stimulating factor-1 receptor (CSF-1R), is mainly studied in cancer for its role in promoting angiogenesis, fibroblast growth, and immune regulation. Although little is known about its effect on ulcers, its high expression in skin fibroblasts suggests a potential role in diabetic ulcer healing [9]. It correlated with insulin resistance [10]. IL-34 is a cytokine that controls macrophage activity and is mainly found in the spleen. It's linked to inflammatory diseases like rheumatoid arthritis, lupus, and inflammatory bowel disease, and is strongly associated with insulin resistance [11].

The aim of this study was to evaluate and compare the diagnostic sensitivity of interleukin-34 (IL-34) and interleukin-17A (IL-17A) in patients with diabetic foot ulcer (DFU), and to determine which biomarker is more effective in identifying the condition.

Materials and Methods

Patients

This study was a case- control study, which involved 100 participants divided into two groups: The first group is the cases group, which consists of 50 (34 males and 16 females), whose ages ranged from 35 to 78 years old patients with diabetic foot ulcer who attended to Al-lmam Al-Hassan Center for Endocrinology and Diabetes in the holy city of Karbala during the period extended from December (2024) to March (2025) and the patients were previously diagnosed by doctors specialized in endocrinology and diabetes consultant. The second group is the control group, consisting of 50 healthy people (35 males and 15 females), whose ages ranged from 35 to 70 years old. A questionnaire was used to collect information from participants, including family history, hypertension, and cardiovascular disease.

Inclusion criteria: All patients with diabetic foot ulcer were diagnosed based on the presence of an ulcer, which is a break in the skin, often associated with neuropathy and/or peripheral artery disease according to the Inter-Society Working Group on the Diabetic Foot (IWGDF) provides specific guidelines, emphasizing a comprehensive approach to diagnosis and treatment [12]. The control group was without any disease.

Exclusion criteria: Patients who have wounds other than diabetic foot ulcer, any type of infection, autoimmune disease, or cancer.

Sample collection

Three millilitres of blood from 100 participants were dispensed into two gel tubes (each one contains 1.5 ml) for some laboratory tests in patients and evaluation of IL-17A and IL-34 serum levels in patients and controls by ELISA test. Serum was collected from blood samples by centrifugation at 3000 rpm for 10 minutes. One ml of blood from 100 participants was dispensed into an EDTA tube for some haematological tests.

Laboratory tests

Other investigations were performed, such as hematological markers which included WBC (ranges 3.5-10 x109/L), lymphocytes (ranges 0.9-5.0 x 109/L), and platelets (ranges 130-400 x109/L). Also, biochemical tests were performed, including HbA1c (4.5%-6.5%), fasting blood sugar (74-120 mg/dl), blood urea (15-45 mg/dl), serum creatinine (0.3-1.3 mg/dl), ALT (0-40 U/L), AST (0-38 U/L), Triglyceride (0-150 mg/dl), Cholesterol (0-200 mg/dl), and LDL (0-130 mg/dl).

Assessment Measurement of IL-17A and IL-34 Levels

The serum levels of IL-17A and IL-34 were measured by using a Sandwich ELISA technique with commercially available ELISA kits (SUNLONG BIOTECH, China), according to the manufacturer's instructions. The assay range for IL-17A is 3.3 -200 pg/ml and 50 -1000 pg/ml for IL-34.

Ethical approval

An ethical certificate from the applicable committees at Karbala Health Directorate was obtained to complete the research with reference number 24-68 on 28 November 2024. All patients' verbal permission was obtained before taking the samples. The research adhered to the ethical principles outlined in the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Statistical analysis

Our investigation was done employing Statistical Package for the Social Sciences software, version 26 (IBM, SPSS, Chicago, Illinois, USA), and the Microsoft Excel 2010 program. The means of the investigated parameters were compared between the two groups using a t-test. Chi-square test was applied to compare between percentages.

Differences among groups were analysed using one-way ANOVA analysis of variance. A receiver operating characteristic (ROC) curve has been applied to evaluate the diagnostic ability of IL-17A and IL-34 as biomarkers to distinguish between di-

abetic foot ulcer cases and controls, and to determine whether IL-17A and IL-34 can serve as predictive factors for diabetic foot ulcers. The results of all tests with p-values <0.05 (two-sided) were considered to be statistically significant.

Results

The results of the current study revealed that the majority of diabetic foot ulcer patients, 37 (74%), had a family history of this disease, while only 13 (26%) had no family history, with significant differences (P=0.0001) (Figure 1). The results of the statistical analysis showed that the highest significant percentage of diseases was for hypertension, where 25 (50%) patients of diabetic foot ulcer patients had hypertension complications as compared with 17 (17%) for cardiovascular disease (P=0.0001) (Table 1).

Table 2 shows a comparison of the hematological markers of the study population. The results of the statistical analysis showed that white blood cell (WBC) count was significantly (P=0.002) higher in the diabetic foot ulcer group, while platelets were significantly (P=0.0459) higher in the control group. On the other hand, the results of the statistical analysis showed non-significant (P=0.40491) differences in lymphocyte levels between diabetic patients with foot ulcers and controls.

Figure 2 illustrates the levels of some laboratory markers in diabetic foot ulcer patients; where the mean of HbA1c was 10.92%, glucose was 289.05 mg/dl, blood urea was 36.63 mg/dl, serum creatinine was 0.86 mg/dl, ALT was 24.90 U/L, AST was 24.70 U/L, triglyceride was 144.22 mg/dl, cholesterol was 163.28 mg/dl, and LDL was 77.24 mg/dl. The serum levels of IL-17A and IL-34 for both diabetic foot ulcer patients and healthy control individuals are shown in Table 3. The statistical analysis revealed that both IL-17A and IL-34 were significantly (P= 0.000 and 0.044, respectively) increased in diabetic patients (43.5048 ± 6.40662 and 84.4276 ± 13.19264, respectively) as compared with healthy individuals (24.4472 ± 11.23773 and 39.2785 ± 4.54062, respectively).

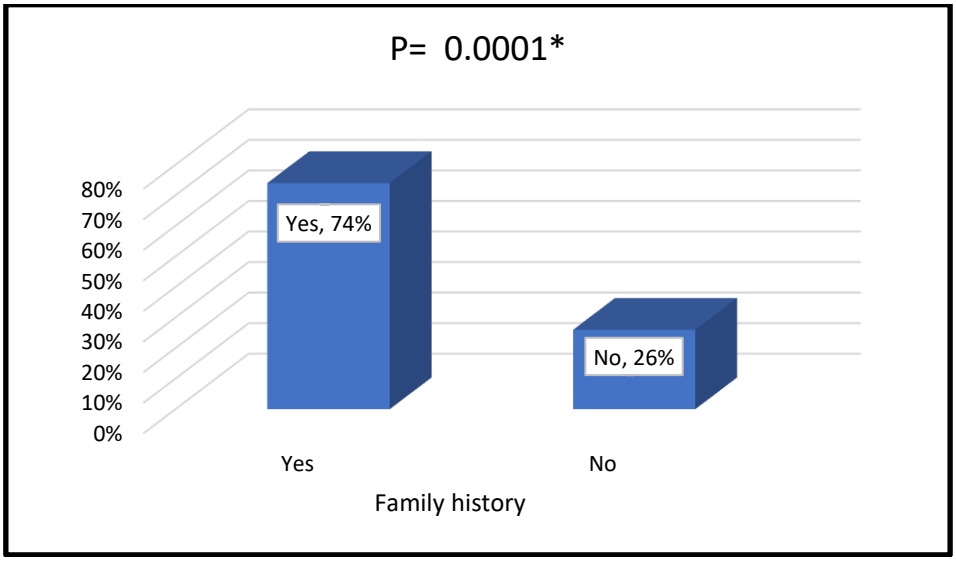

Figure 1: Family history for patients

Table 1: Comorbidities of diabetic foot ulcer patients

Disease	State of patients No. (%)		P-value
	Yes	No	
Hypertension	25 (50%)	25 (50%)	1.000
Cardiovascular	17 (17%)	83 (83%)	0.0001*
P-value	0.0001*	0.0046*	

*Significant difference at the 0.05 level by Chi-square test.

Table 2: Hematological markers for study population

Parameters	Study population Mean ± SD		P-value
	Patients (n=50)	Control (n=50)	
WBC 10^9/L	8.8528 ± 2.85526	7.4590 ± 1.15276	0.002*
Lymphocyte 10^9/L	29.6452 ± 6.67084	30.6858 ± 4.40102	0.40491
Platelets 10^9/L	272.820± 84.02859	298.4600 ± 44.7880	0.0459*

S: Standard deviation
*Significant difference at the 0.05 level by Chi-square test.

The ROC analysis of IL-17A and IL-34 demonstrates significant outcomes, as shown in Table 4 and Figure 3. Regarding IL-17A, the area under the curve (AUC) is 0.638, reflecting a moderate diagnostic ability; sensitivity is 0.32, while the specificity is 0.96, and the cut-off value is 38.95. The p-value is 0.017, indicating that the results were statistically significant. With regard to IL-34, AUC is 0.743, revealing a good diagnostic ability. The sensitivity is 0.78, and the specificity is 0.64, and the cut-off value is 36.5. The p-value of 0.0001 demonstrated highly statistically significant outcomes.

Discussion

The results of the current study showed significant differences in the family history of patients. There was 74% of patients had a family history, while only 26% had no family history. Consistent with the findings of Xiong *et al.* (2020) revealed that diabetic foot complications (DFCs) among T2DM patients were associated with family history of diabetes (FHD), with a relationship between FHD and DFCs, especially of the different numbers of relatives with diabetes, in which the number of patients with one or more relatives with diabetes led to fold increases in the risk of DFCs compared with those without FHD [13]. Tuglo *et al.* (2022) also discovered that diabetic patients who had a family history of diabetes were 4.7 times more likely to develop diabetic foot ulcers than those without a family history [14]. A higher prevalence of DFU in patients with a family history of diabetes underscores the need for targeted screening and prevention strategies in this population. However, to better understand the interplay between genetic predisposition, environmental factors, and clinical outcomes in DFU patients is needed.

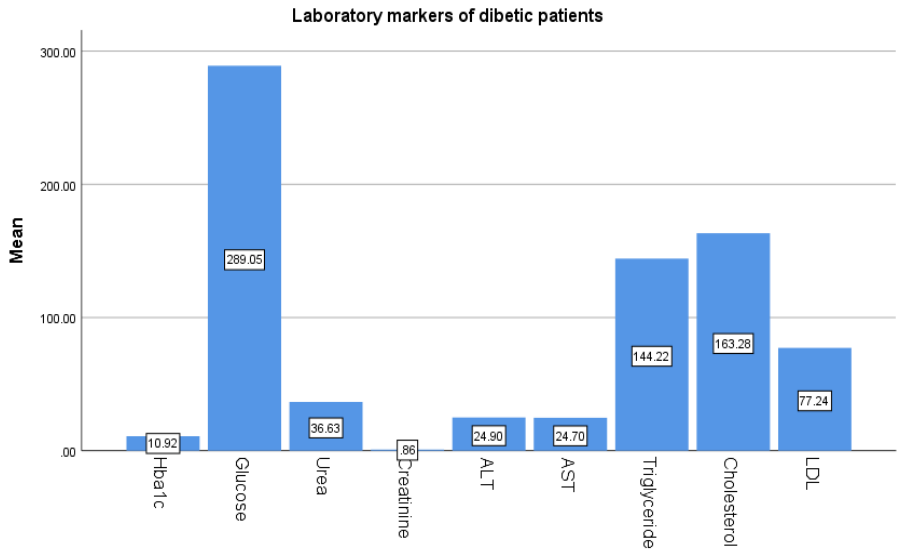

Figure 2: laboratory Parameters in diabetic foot ulcer patients

Table 3: Immunological parameters for study population

Parameters	Study population Mean ± SD		P-value
	Patients (n=50)	Control (n=50)	
IL-17A Pg/ml	43.5048 ± 6.40662	24.4472 ± 11.23773	0.000*
IL-34 Pg/ml	84.4276 ± 13.19264	39.2785 ± 4.54062	0.044*

S: Standard deviation
*Significant difference at the 0.05 level by Chi-square test.

Table 4: ROC curve of immune marker in patients

Markers	AUC	Sensitivity	Specificity	Cut-off	P-value
IL-17A	0.638	0.32	0.96	38.95	0.017*
IL-34	0.743	0.78	0.64	36.5	0.000*

AUC: area under the curve
*Significant difference at the 0.05 level by chi-square test.

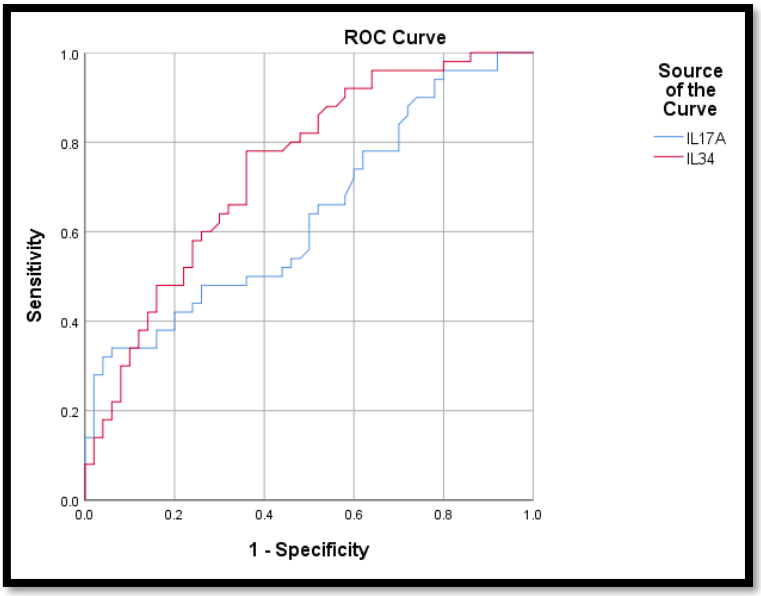

Figure 3: Receiver operating characteristic (ROC) curve for immune marker in patients

The present study observed the highest significant percentage of hypertension complications in diabetic foot ulcer patients as compared with cardiovascular disease. This result aligns with the research done by Dekker *et al.* (2016) revealed that hypertension was associated with diabetic foot ulcer [15], Also, Luo *et al.* (2024) discovered that the complications and comorbidities of diabetes may increase the incidence of lower extremities amputation among patients with DFU. Hypertension, cardiovascular disease, and renal disease, which were included in the study, all had substantial impacts on the incidence of lower extremities amputation (LEA) in DFU patients [16]. On the contrary, Lu *et al.* (2021) found that hypertension was not a risk factor for lower extremities amputation of patients with diabetic foot ulcer [17]. The discrepancy between the recent study and the previous study regarding hypertension may be attributed to differences in study design, sample characteristics, or population-specific risk factors.

In the present study, white blood cell (WBC) count was significantly higher in the DFU group. The investigation led by Gong *et al.* (2023) resembled the present study; they discovered that higher white blood cell within the amputated patients [18]. Also, Luo *et al.* (2024) showed white blood cell count as a risk factor for lower extremities amputation [16]. Increased white blood cell counts indicate a more serious infection in patients; chronic and severe infections can cause exudation and oedema, which delay the creation of granulation tissue and cause wounds that don't heal, ultimately leading to amputation.

The control group of the current study showed a significantly higher platelet count than DFU patients. Yang *et al.* (2023) revealed that decreased platelet counts were indicative of impaired wound healing and poorer prognosis; this finding is aligned with the current study [19].

The current study did not find significant differences in lymphocyte, as proved by another study, Ali (2023), which found that the correlation was non-significant between lymphocyte and IL-17A in DFU patients [20].

In the current study, the HbA1c level and glucose level indicate poor glycemic control, which is a well-established risk factor for DFU development and progression. Chronic hyperglycemia leads to endothelial dysfunction, neuropathy, and impaired wound healing, creating a favourable environment for infections and ulcer formation. This study was in the same line as the study done by Akyüz *et al.* (2023), who emphasized that HbA1c levels are strongly associated with increased DFU severity and amputation risk [21]. Also, a study conducted by Zaki *et al.* (2024) found that patients with poor glycaemic control are more likely to develop DFUs and are more likely to develop diabetic foot lesions [22]. In contrast to the current study, Bhat *et al.* (2024) demonstrated that the presence of a wound did not show any association with increasing HbA1c levels [23]. Also, Lee *et al.* (2024) found HbA1c levels were significantly lower in diabetic foot patients [24]. The difference between the current study and other studies may be due to several reasons, such as the type of study, differences in patient characteristics (like age or diabetes duration), or how the wound was assessed. Also, location and quality of healthcare may play a role.

In addition, the blood urea level was elevated, and creatinine was within the normal range. Elevated blood urea levels may indicate early renal stress, which is common in diabetic patients due to hyperglycemia-induced nephropathy. Although creatinine levels are normal, diabetic patients are at high risk for chronic kidney disease (CKD). A study by Yao *et al.* (2024) indicated that patients with elevated levels of creatinine and urea had an increased chance of amputation. Regular monitoring of renal parameters is essential to prevent CKD progression [25].

The ALT and AST levels in this study were within normal ranges. In contrast to earlier finding of a study by Wang *et al.* (2022) showed that the blood ALT and AST levels of DFU patients were significantly higher than those of non-foot ulcer (NFU) patients [26].

Triglycerides, cholesterol, and LDL were within normal ranges in this study. This result was in agreement with study accomplished by Yao *et al.* (2024) who revealed that cholesterol, triglycerides, and low-density lipoprotein were not statistically significant in results of patients with major and minor amputation, Similar to previous studies, cholesterol, LDL and triglyceride were also not statistically associated with diabetic foot with [25]. A study by Lee *et al.* (2024) revealed that in the case of LDL, there was no difference in DM foot patients compared with healthy people [24]. While a study done by Ulloque *et al.* (2022) was contrary to the current study, when found that the higher values of total cholesterol (TC), low-density lipoprotein (LDL), and triglycerides were associated with a higher risk of developing DFU [27].

The present study demonstrated a significant elevation in serum levels of IL-17A and IL-34 among DFU patients compared to healthy controls. The results of the study conducted by Ali (2023) illustrated that IL17A had a crucial role in the development of diabetic mellitus and its complications, such as DFU [20]. Also, Yousefidaredor *et al.* (2014) found that studies have demonstrated that high levels of IL-17A are associated with chronic inflammatory and autoimmune diseases [7]. IL-17A levels in peripheral serum and atrial fluid were significantly higher in non-proliferative diabetic retinopathy (NPDR) and proliferating diabetic retinopathy (PDR) patients than in NPDR patients in subgroup analyses, and detection of peripheral serum IL-17A concentrations could help to assess the risk of progression from NPDR to PDR, these findings were reported by Li *et al.* (2024) [28]. Regarding IL-34, a study of Piao *et al.* (2019) found that IL-34 expression is highly increased in the serum of patients with gestational diabetes mellitus (GDM) [29]. In addition, there was a positive association between serum IL-34 and insulin resistance and glucose concentrations. Dikilitaş *et al.* (2022) reported that the IL-34 secretion is increased in the serum and synovial fluids of rheumatoid arthritis patients, with a pathogenesis similar to that of periodontitis [11]. On the contrary, Zheng *et al.* (2022) found that IL-34 expression was lower in patients with non-healing DFU than those with healing DFU [9]. The difference between current findings and previous studies regarding IL-34 levels may be due to variations in the stage or classification of the ulcers studied.

The current results showed varying levels of diagnostic utility for the two markers. For IL-17A, the area under the curve (AUC) indicated a moderate diagnostic ability, and the result was statistically significant. A study conducted by Yang *et al.* (2023) showed the presence of a statistically significant difference in IL-17A in type 1 and 2 diabetes mellitus between the DFU and control group [19]. This suggests that while IL-17A may not be highly sensitive as a standalone screening marker, it has strong specificity, making it potentially useful in confirmatory diagnostics or in combination with other markers. Its elevated levels in a small number of patients may reflect acute inflammatory changes or variability in immune response among DFU patients.

IL-34 showed a more promising profile with an AUC, reflecting a good diagnostic ability, with a highly significant result. These findings indicate that IL-34 is a more balanced and reliable biomarker for distinguishing between DFU patients and healthy controls. Its relatively high sensitivity and acceptable specificity make it a suitable screening tool and a potentially valuable biomarker for early detection and monitoring of DFU-related immune alterations.

Conclusions

This study demonstrated that serum IL-34 levels were significantly higher in patients with diabetic foot ulcer compared to IL-17A. IL-34 showed greater sensitivity and diagnostic performance, suggesting its potential role as a superior biomarker for early detection and monitoring of diabetic foot ulcers. Further studies on larger populations are recommended to validate these findings. The statistically significant rise in both IL-17A and IL-34 indicates their potential as biomarkers for inflammation severity in DFU and might have offered insights into new therapeutic targets aimed at modu-

lating the immune response to promote wound resolution. Further investigations were warranted to elucidate the precise mechanisms through which these cytokines had contributed to DFU progression and to explore their value in clinical prognosis and treatment monitoring.

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