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ORIGINAL RESEARCH

Cost-Effectiveness Analysis for Managing Diabetic Foot Ulcer (DFU) in USA: Platelet-Rich Plasma (PRP) vs Standard of Care (SoC)

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Purpose: Chronic skin ulcers in diabetic foot patients are a significant health concern. Diabetic foot ulcers (DFUs) significantly threaten the health and longevity of individuals with diabetes, leading to severe complications like infection and amputation and contributing to high morbidity and mortality rates. Given the severe implications, practical strategies to prevent and manage DFUs are crucial to reducing amputation rates. Platelet-rich plasma (PRP) has emerged as a popular treatment option due to its properties that mimic the body's natural healing process. The objective of the study was to evaluate the cost-effectiveness of PRPR vs standard of care in US context.

Methods: Decision analytical model was used to synthesize clinical and economic parameters. In detail a CEA analysis was employed using a Markov decision-making model to evaluate patients with chronic DFUs lasting over three weeks and at high risk for orthopedic complications. The study assessed the effectiveness of different treatments, measured in quality-adjusted life years (QALYs), and reported costs in 2023 dollars using a micro-costing approach alongside a clinical trial.

Results: The study concluded that PRP gel is a cost-effective treatment for non-healing DFUs, resulting in lower care costs over one year compared to other treatments and cost savings over five years.

Conclusion: Thus, PRP treatment is a promising and practical option, improving patient outcomes and reducing healthcare costs. It is an attractive choice for healthcare providers and insurers in managing non-healing diabetic foot ulcers.

Keywords: cost-effectiveness analysis, wound management, platelet-rich plasma, DFUs, diabetic foot ulcer, Ulcer

Introduction

The presence of a chronic non-healing ulcer is a considerable health concern, with a global prevalence range of 1.9 to 13.1%.[1,2] The incidence of chronic ulcers is anticipated to rise as the population ages, as advancing age makes the healing process slower.[3] One of the leading causes of non-healing ulcers is diabetes. In particular, one of the most severe long-term complications of diabetes mellitus is the development of foot ulcers as a consequence of the sustained effect of peripheral neuropathy and vascular insufficiency.[4] Approximately 18.6 million people worldwide are affected by diabetic foot ulcers yearly, including 1.6 million people in the United States.[5] A recent study, which investigated the changes in Medicare spending on chronic wounds between 2014 and 2019, revealed a noteworthy increase in the prevalence of DFU infections in both sexes. The rates of DFU infections among males increased from 3.2% to 4.7%, while those among females increased from 3.1% to 4.2%,[6] significantly impacting the quality of life of 2.5% of the US population. The meta-analysis by Zhang et al (2017)[5] on the global prevalence of diabetic foot ulcers shows that globally, 6.3% (95% CI: 5.4–7.3%) of people with diabetes suffer from foot ulcers. The prevalence was higher in males (4.5%, 95% CI: 3.7–5.2%) than in females (3.5%, 95% CI: 2.8–4.2%), and higher in patients with type 2 diabetes (6.4%, 95% CI: 4.6–8.1%) than in those with type 1 diabetes (5.5%, 95% CI: 3.2–7.7%). Belgium has the highest prevalence of 16.6% (95% CI: 10.7–22.4%), followed by Canada with 14.8% (95% CI: 9.4–20.1%), North America with 13.0% (95% CI:

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10.0–15.9%), Africa with 7.2% (95% CI: 5.1–9.3%), Asia with 5.5% (95% CI: 4.6–6.4%), Europe with 5.1% (95% CI: 4.1–6.0%), Oceania with 3.0% (95% CI: 0.9–5.0%) and Australia with the lowest prevalence of 1.5% (95% CI: 0.7–2.4%).

Estimates suggest that Medicare spending for all wound types falls between $28.1 and $96.8 billion.[7] Nussbaum's study[8] found that surgical wounds and diabetic foot ulcers are the most expensive, costing $11.7-$38.3 billion and $6.2-$18.7 billion, respectively. Diabetic foot ulcers, complicated by neuropathy, often lead to infections and prolonged healing, making them a significant risk factor for lower limb amputation.[9]

According to recent research, approximately 12% of individuals who are diagnosed with diabetic foot ulcers require amputation of the lower extremity.[10–12] Armstrong's[13] data indicates that diabetic foot ulcers significantly increase mortality in individuals with diabetes. They precede 80% of diabetes-related lower extremity amputations, with half becoming infected and 20% of moderate to severe infections leading to amputation. The 5-year mortality rate is about 30% for those with ulcers and over 70% for those with significant amputations. Mortality is higher among those with ulcers (231 deaths per 1,000 person-years) compared to those without (182 per 1,000 person-years). Each year, approximately 150,000 people in the United States undergo nontraumatic leg amputations, with most cases occurring among diabetic patients.[14]

In the US, diabetic foot ulcers (DFU) are responsible for 83% of all significant amputations and 96% of all minor amputations. DFUs significantly increase the cost of care, resulting in $1.38 billion per year compared to non-DFUs at $0.13 billion per year ($p < 0.001$).[15]

Between 2000 and 2009, there was a decline of around 40% in the amputation rate among patients with diabetes. However, from 2009 to 2015, there was a subsequent increase of 50% in the amputation rate.[14] According to a previous study,[16] a lower limb is amputated due to diabetes every 30 seconds. Treating diabetic foot averages $8659 per patient annually.[17] Furthermore, in the United States of America, the cost of medical treatment for diabetic foot diseases ranges from nine to thirteen billion dollars. This cost is an additional financial burden associated with diabetes, which already incurs significant expenses.[18]

Therefore, it is clear that ulcers, besides causing a significant decline in patients' quality of life, lead to high therapeutic costs.[19]

Chronic ulcers pose a significant financial burden for the patient and the healthcare system. With the population's increasing age, rising cases of diabetes and obesity worldwide, and the persistent problem of infection, chronic wounds will continue to be a substantial clinical, social, and economic challenge.[7,20,21]

The escalating prevalence of diabetes across several nations has resulted in a significant and growing public health challenge of foot ulcers.[22]

Thus, the International Diabetes Foundation is currently undertaking measures to raise awareness regarding diabetic foot problems. This initiative responds to the condition's significant medical, social, and economic implications.[23]

The only solution is to evaluate strategies that improve wound prevention, management, and reduce amputations.

Regenerative medicine represents an innovative approach to promoting wound healing by utilizing autologous growth factors. Modern techniques now allow for the straightforward production of these growth factors by collecting a patient's blood and processing it with specialized devices to create platelet-rich plasma (PRP),[24] which is characterized by its rich and complex secretion profile, including more than 300 proteins.[25] PRP is rich in thrombocytes, and its α-granules contain numerous growth factors like PDGF, TGF-β1, TGF-β2, platelet factor IV, interleukin-1, platelet-derived angiogenesis factor, VEGF, EGF, insulin-like growth factor, osteomacin, osteonectin, fibrinogen, vitronectin, fibronectin, and thrombospondin-1.[26]

Autologous PRP gel is gaining widespread application across numerous surgical specialties, particularly for addressing various soft-tissue and hard-tissue defects, enhancing bone regeneration, and treating persistent, nonhealing wounds.[27.]

It has been demonstrated that plasma growth factor (PGF), such as platelet-derived growth factor (PDGF), significantly shortens treatment duration and leads to healing in approximately 80% of wounds.[28–31] Many authors[28–31] found that platelet release has improved healing rates compared to standard remedies. On the other hand, other studies[28,29] found no significant difference in the healing outcome of leg ulcers between treatment groups with platelet release and control groups (placebo). An extensive review was performed by Picard et al 2015. They carried out a PubMed and Cochrane search (1978–2015), including all studies assessing the clinical effect of PRP on the healing of diabetic chronic wounds. The screening retrieved 7555 articles, and 12 studies were included. Of six randomized studies, five found

significant benefits for using PRP on diabetic chronic foot ulcers. The authors concluded that 87.5% of controlled studies found a significant benefit for the adjunction of PRP to treat chronic diabetic wounds.

As PRP may be beneficial, they suggest using it on diabetic ulcers that remain unhealed after standard treatment. Platelet-derived growth factors can play a critical role in wound healing by driving key processes such as chemotaxis, cellular proliferation, and angiogenesis,[32] supporting tissue repair[33] and promoting cell recruitment and differentiation.[34]

Such emerging cellular therapies can serve as an adjunctive component within a standardized, high-quality treatment plan.[35]

Recent meta-analyses and review articles further underscore the therapeutic potential of PRP in chronic wounds, demonstrating benefits such as complete wound closure, reduced wound surface area, minimized scarring, and a lower incidence of infections.[36–47] In particular, the review performed by OuYang[48] found that PRP significantly improved the healing rate (OR = 4.37, 95% CI 3.02–6.33, P < 0.001) and shortened the healing time (MD =−3.21, 95% CI−3.83 to−2.59, P < 0.001) of patients with DFU when compared to the conventional treatment.

These findings are consistent with the meta-analysis performed by Syafira[49] that revealed that PRP exhibited a healing rate that was twice as high as the control group (Relative Effects (REs) = 2.338; 95% Confidence Interval (CI) = 1.056 to 1.857, *P* = 0.019). Additionally, the healing time was shortened by two days (REs = −2.815; 95% CI = −3.252 to −0.576, *P* = 0.005), and there was a difference of 0.482 cm² in the reduction of ulcer area between the two groups (REs = 0.482; 95% CI = −2.428 to 4.002, *P* = 0.630).

Also Deng[50] finds that autologous PRP has a significant positive effect on the healing rate (RR = 1.42, 95% CI 1.30–1.56, P < 0.001), reduces the healing time (MD = − 3.13,95% CI − 5.86 to − 0.39, P < 0.001), accelerates the reduction of ulcer area (MD = 1.02, 95% CI 0.51–1.53, P < 0.001), decreases the rate of amputation (RR = 0.35, 95% CI 0.15–0.83, P < 0.001), and does not increase the incidence of adverse events (RR = 0.96, 95% CI 0.57–1.61, P > 0.05) when compared to conventional therapy.

According to these data, PRP used to treat Diabetic Foot Ulcers (DFUs) has shown promising clinical results; however, the costs associated with this treatment may be higher than standard therapy. Therefore, its cost-effectiveness must be evaluated before implementing this approach in health systems. Only a few studies have directly dealt with the relationship between the costs and the results of PRP versus standard care, and, in addition, economic evaluations in parallel with clinical studies have yet to be reported. Two studies before 2014 found PRP treatment to be cost-effective or even dominant compared with usual care.[30,51,52] Recently, Linertová et al found that, in a 5-year time horizon, PRP treatment for DFU could be considered a cost-effective or even a cost-saving alternative in Spanish healthcare settings, depending on the method of obtaining the PRP (commercial kit versus manual method) and, to a large extent, on the price of the kit used. Consequently, these authors called for future studies on the effectiveness and costs of specific devices or methods to be used as inputs for more specific cost-effectiveness models.[53]

This study aims to fill this gap by conducting a cost-effectiveness analysis of a specific PRP preparation procedure for treating DFUs versus standard care, with a 1-year time horizon. The methodology adopted follows a previous study carried out in the French context.[54] This analysis provides specific evidence and insights for clinical and managerial decision-making in a US setting.

Materials and Methods

Treatment

The present study focuses on analyzing autologous PRP gel in promoting the healing of chronic deep diabetic foot ulcers, classified as 3 A stage according to UT classification, comparing it with the standard of care. (Soc). Soc includes debridement, infection control, management of comorbidities, and off-loading.

According to clinicians' opinions and previous studies, a series of assumptions are made for the model.[55] During PRP treatment, a gel is created from the patient's blood. In the French study of reference, this practice is done by extracting platelet-rich, leukocyte-poor plasma with the help of a commercial kit called Regenkit (RegenLab, Switzerland). The kit includes three tubes (2 BCT and 1 ATS) used to produce the PRP gel. Then, PRP is used for wound medication. The treatment lasts six weeks or less if the wound has closed. Patients in the PRP gel group may receive more than one application, as decided by the investigator. The primary efficacy endpoint for wound closure is measured at six weeks, and efficacy is also evaluated during follow-up visits at nine and twelve weeks.

For the PRP arm, the patients only need to change the protective compress once a week at home. However, the dressing must be changed once daily at home for the control group.

In Table 1, we summarize the main parameters used.

Table 1 Data Collected

	Brand	Description	Price	Amount	Unit cost	Coefficient of Use	Cost Per Application
PRP							
Jelonet (5″x9″)	Carbou	Box of 25	25.99	1	2.6	0.33	0.85
Adaptic (4″x4″)	Dr. Med	Box of 25	21.99	1	2.2	0.33	0.73
Grassolind (4″x4″)	Carbou	Box of 25	20.99	1	2.1	0.33	0.7
Sterile non-woven sponges	Care science	Box of 100 bags	25.49	10 compresses	2.6	1	
Physiological serum	Braun	Bottle (250mL)	13.47	1 bottle/10 patients	1.35	1	1.35
Steristrip (4″x4″)	Minnesota 3M	10 stripe pouch	3.61	1 pouch	0.36	1	0.36
Adhesive fixing tape	Niceful	1 pansement	1.44	1	1.44	1	1.44
Tape	Niceful	1 pansement	1.44	1	1.44	1	1.44
Total medication cost PRP							**9.47**
COMPLEX DRESSING							
Mediset post-op dressing	Euromed	Box of 6	9.99	1 set/patient	1.66	1	1.66
Physiological serum	Braun	Bottle (250mL)	13.47	1 bottle /10 patients	1.35	1	1.35
Sterile non- woven compresses	Care science	100	25.49	10 compresses	2.6	1	2.6
Adhesive fixing tape			1.44	1	1.44	1	1.44
Tape			1.44	1	1.44	1	1.44
Betadine gyneco 473mL	Dynarex	Bottle	14.56	1 bottle/15 patients	0.97	1	0.97
Mépilex (4″x4″)	Medway	Box of 10	29.99	1	3.00	0.175	0.52
Mépilex épais (6″x6″)	Medway	Box of 5	15.21	1	1.5	0.175	0.26
Impregnated compressed (2″x2″)	Dukal	Box of 12	18.91	2	3.15	0.175	0.55
Urgotul (4,25″x4,25″	Areza	Box of 10	27.99	2	5.6	0.175	0.98
Cutimed Sorbion (6″x6″)	Areza	Box of 5	20.99	1	2.1	0.07	0.14
Vliwlasorb (4″x4″)	Lohmann	Box of 10	25.77	1	2.58	0.07	0.18
Sorbact (wound contact layer) (4″x4″)	Cutimed Sorbact WCL	Box of 10	70.84	1	7.09	0.07	0.5
Super Absorbent Dressing for Wound Care (4″x5″)	Simpurity	Box of 10	23.36	2	4.7	0.05	0.23
Super Absorbent Dressing for Wound Care (8″x10″)	Simpurity	Box of 10	30.00	2	6	0.05	0.3
Total medication cost Complex dressing						1	**13.46**

Model Description

A Markov model was utilized to conduct a cost-effectiveness analysis on a theoretical cohort of patients with chronic diabetic foot ulcers (DFU) lasting more than three weeks and facing a high risk of orthopedic complications. These patients had ulcers classified as grade 3A according to the UT classification, indicating deep ulcers reaching the bone, including tunneling and perforating wounds.

The decision-analytic model enabled us to establish a framework and integrate evidence from the "Le Creusot" study[55] and existing literature to generalize the findings. The flexibility of the Markov model made it particularly useful for modeling chronic conditions that progress over months or years. It can account for ongoing risks and recurrent events over time.[56]

The first step involved defining DFUs (Diabetic Foot Ulcers) based on specific states that encompass all relevant health outcomes, with transitions between these states governed by transition probabilities. In this study, the Markov model included six potential health states: two temporary states, three standard states, and one absorbing state. These states were: (1) initial complete DFU treatment; (2) persistent DFU; (3) fully healed DFU; (4) amputation; (5) post-amputation; and (6) death from any cause and surgery. In the initial stages of the application model, patients with DFUs would receive the initial treatment based on one of the following strategies: PRP combined with the best SoC or SoC alone. Hypothetical patients started in state one and moved through predefined health states. Each clinical state was linked to a cost and effectiveness estimate. Hypothetical patients accrued costs and QALYs (quality-adjusted life years) corresponding to the time spent in each clinical state during the simulated three-month period. The cycle length was one week, and the time horizon was one year.

Patients received their initial complete treatment during the first phase, after which they transitioned to the second state with a 100% probability. In the second state, also known as persistent DFU, patients received weekly care. For PRP treatment, some patients might need a new complete treatment, which is more costly than the weekly care. We modeled the need for a second treatment as a transient event rather than a state. Therefore, we used transition rewards to associate a one-time cost with the patient requiring a second treatment. It is crucial to note that the need for a new treatment is not a state itself and does not impact state transitions. However, it may result in additional costs and/or disabilities, unlike traditional care involving daily dressing changes until the wound heals.

In state 2, the home nurse for the PRP arm opens the dressing and checks the cleanliness of the primary dressing. This is performed once a week, according to the "Le Creusot" study[55] protocol, unless complications arise. If the dressing is clean, the nurse replaces the secondary dressing. If not, a second complete treatment is scheduled. Meanwhile, in state 2, for the standard treatment arm, a home nurse performs a complex dressing change daily by cleaning and dressing the wound five days a week.

Progressing to state 3, patients will incur the costs and benefits of a fully healed ulcer. However, there is a risk of recurrence for diabetic patients, which may necessitate new medications and a transition from the state of complete wound healing to relapse. Finally, state 6 is an absorbing state that includes individuals who die from any cause (life table), including those who succumb to surgery. The results regarding the incremental cost-effectiveness ratio (ICER) are presented.

Cost Inputs

The costs related to healthcare states and transition costs in the Markov model have been expressed in dollars for 2022, as presented in Table 1. We have estimated the costs using a micro-costing approach that considers the resources used in the "Le Creusot" study.[55] These costs reflect the viewpoint of the US healthcare system.

We have made some estimations to determine the average cost of a simple dressing (PRP group) and a complex dressing (SoC group). Jelonet, Adaptic, Grassolind, and a serum secondary dressing were used for a simple dressing. Depending on the wound characteristics, different product families were used for a complex dressing. The utilization rate of hydrocellular dressing was 70%, superabsorbent hydrocellular dressing (Cutimed, Wilsabord, Sorbact) was 20%, and Urgostart was used in 10% of the cases. The main parameters used are summarized in Table 1.

In State 1, the PRP cost is due to the use of Regent BCT-1 (X2) and ATS (X1) kits, along with the cleaning procedure and medication and the time spent by the nurse. On the other hand, the comparator's cost is due to the cost of complex dressing, cleaning procedures, and nurse time.

In State 2, the PRP cost is due to the medication's repair and the nurse's time. The comparator's cost is due to the cost of complex dressing, cleaning procedures, and nurse time multiplied by five times per week. In Table 2 we reported the costs used in the model.

Utility Inputs

Quality of life assessments for six potential health states were based on general health status profiles, which, though less sensitive than illness-specific scales, allow for comparisons beyond specific diseases. Common generic preference-based measures include the EuroQol EQ-5D, SF-6D, and HUI.[59] These questionnaires generate a score (0 for dead, 1 for perfect health) based on public values, used to calculate QALYs (Quality-Adjusted Life Years). The advantage of these methods is their ability to compare outcomes across different health conditions and assess the economic impact of health interventions, aiding informed decision-making. This analysis utilized the EuroQol instrument and data from Redekop et al (2004), using the time trade-off method (Table 3) to estimate utility weights for health states related to diabetic foot ulcers (DFUs).

The source used in this study has been previously used to provide quality-of-life estimates for a cost-effectiveness analysis of a negative pressure device for treating DFUs. Quality-Adjusted Life Years (QALYs) were calculated by multiplying the quality-of-life utility weight for a particular health state by the number of years spent there.

Table 2 Data Used in the Model: Costs

Parameters	Base Case Value ($)	Min	Max
Nurse/minute ($) BLS	$1.05	$0.52 (South Dacota)	$1.06 (California)
		$31.01/hourly wage	$64.10/hourly wage
Blood sampling Tariff – Phlebotomists (https://www.payscale.com/research/US/Job=Phlebotomist/Hourly_Rate)	$0.29 ($17.09 an hour 2022)	$0.22	$0.37
		$13.09/hour	$22.16/hour
Time resources			
Minutes to prepare PRP and dressing (complete procedure)/day	30 minutes	25	35
Minutes for checking the wound treated with PRP/weekly	15 minutes	10	20
Minutes to prepare Hydrocolloid and dressing/daily	20 minutes	15	25
Material used			
RK-WG-2 kit (2 PRP tubes, 1 ATS tube, no accessories) (Market price)	870	750	990
Cleaning and Secondary Dressing			
PRP treatment	9.5	7.5	11.4
Standard of care	13.46	10.8	16.2
Amputation			
Surgery cost[57]	$60,012	$46,802	$73,222
Annual Post surgery costs (Medicare Service reimbursement)[58]	$55,000		
PRP one complete procedure total cost	916.77		
PRP weekly routine check total cost	9.5	7.5	11.4
Hydrocolloid procedure weekly total cost	67.3	54	81

Table 3 Data Used in the Model: Effectiveness (at 3 Months) Source: Redekop et al, in 2004[60]

Health State	Base Case (QALYs)	Min	Max
No active ulcer	0.84	0.81	0.87
Active ulcer	0.70	0.66	0.75
One foot amputated	0.68	0.63	0.72
Amputation	0.31	_	_

Probabilities

The probability of healing in this study was estimated based on the percentage of ulcers that were completely healed after 12 weeks of treatment. The "Le Creusot" study[55] found that 77.3% of patients who received PRP care had fully healed ulcers, while only 35.1% of patients who received usual care had healed ulcers. However, in our cost-effectiveness analysis, we took a conservative approach and used data from a meta-analysis of five clinical trials. This analysis found that the success rate for healing with PRP was 58.33%, compared to 50.31% for usual care.[40] The study conducted in "Le Creusot" study[55] found that out of the patients involved, 27 received one injection, 17 received two injections, and two individuals received an unknown number of applications. On average, patients received 1.46 PRP treatments. Based on the study, there is a 50% chance of receiving a second complete treatment during a cycle. This is a conservative estimate as the actual probability of receiving a second complete treatment, according to the study, is 0.2. To create a more generalized model, the risk of amputation and relapse were also included. Amputation is considered a temporary state that leads to a post-amputation state. The probability of amputation was taken from the Moulik study[61] and adjusted according to the model cycles, which are one week long. The 'new occurrence' probability was taken from the Eurodiale study.[62]

Sensitivity Analysis

Deterministic sensitivity analysis was conducted to evaluate the impact of parameter uncertainty on the model's results (Table 4). A sensitivity analysis was performed on the most critical parameters of the model. This analysis helps to deal with different uncertainties, such as model uncertainty, parameter uncertainty, and heterogeneity. One-way DSA and tornado analysis were run for every parameter, with a minimum and maximum scenario reported.[62]

Moreover, probabilistic sensitivity analysis was conducted through a Monte Carlo simulation, performing 10,000 cases. This analysis was carried out to assess the uncertainty around the ICER and the probability of the PRP therapy being cost-effective at various willingness-to-pay thresholds. A probability distribution was assigned to each model input parameter to describe the different values the parameter can have with different probabilities. The effectiveness and probabilities were modeled with Beta distributions, while costs were represented as Gamma distributions, as

Table 4 Data Used in the Model: Probability of Healing (at 3 Months)

Parameters	Base Case (%)	Min	Max
Probability of healing[48] PRP Hydrocolloid	0.58 0.50	0.46 0.40	0.69 0.60
Recurrence[62]	0.068	0.054	0.081
Amputation[61]	0.014	0.011	0.017
Surgery mortality[61]	0.0029	_	_

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recommended in the literature.[63] For the parameters cited in literature where standard error was not estimated, a general standard error of 25% of the mean value was assumed.[62]

To conduct all the analyses about the study, we utilized the advanced software tool TreeAge Pro 2021. This cutting-edge software enabled us to carry out complex and detailed analyses, providing accurate and reliable research results.

It was deemed unnecessary to seek ethical approval for the study, as secondary data was used.

Results

In the base case scenario (1 year), the average cost per QALY is around $133.21 for the comparator and $140 for PRP, respectively. PRP treatment has an ICER of $2,801, which is lower than the classical wtp threshold, indicating the dominance of the PRP therapy.

A one-way sensitivity analysis was performed for the main parameters to determine each parameter's influence on the results (Table 5).

Table 5 One-Way Sensitivity Analysis

Variable Description	Variable Low	Variable Base	Variable High	Low (ICER)	High (ICER)
Number of medications Soc	3	5	7	−10,011.82	15,615.05
Total Procedure Costs PRP	733.41	916.77	1100.12	−4,163.56	9766.79
Number of medications PRP	1	1	4	2,801.61	13,655.94
Soc preparation time	10	20	20	2,801.61	12,562.28
Nurse cost (per minute)	0.52	1.05	1.06	2,648.61	10,910.71
Regen kit price	750	870	990	−1,756	7,360
Total wound cleaning procedure cost (Soc)	10.77	13.46	16.15	301.02	5,302.20
Amputation probability	0.00044	0.00117	0.0013	2,390.02	5,392.14
Single medication time (PRP) following the complete procedure	0	15	15	542.09	2,801.61
Qalys for active ulcer	0.66	0.7	0.75	2,359.10	3,659.69
Qalys for NO active ulcer	0.81	0.84	0.87	2,368.68	3,428.19
Amputation surgery cost	46,800	60,012	73,222	2,293.02	3,310.28
Relapse probability	0.00464	0.0058	0.00696	2,538.17	3,068.66
Post amputation costs	830.4	1,038	1,245.6	2,541.95	3,061.27
Total Procedure time PRP	24	30	36	2,562.29	3,040.93
Blood sampling procedure cost	0	5.8	4.72	2,581.28	2,76077
Total wound cleaning procedure cost (PRP)	9.27	9.47	9.67	2,765.32	2,837.90
Probability of dying (surgery)	0	0.00024	0.0029	2,798.73	2,801.87
Probability of a new PRP complete procedure	0.1	0.2	0.5	−48,137.78	2,801.61
Healing probability (Soc)	0.04	0,05	0.06	−7,985.09	2801.61
Healing probability (PRP)	0.05	0.058.	0.07	−6,475.40	2,801.61

The analysis shows that the most sensitive parameters are the number of weekly dressings performed for the SoC, the PRP complete procedure, and the number of core PRP dressings.
According to the one-way analysis, we highlight that:

1. The number of SoC dressings ranges from a minimum of 3 to a maximum of 7. If the dressings performed are 3 instead of the base case 5, the ICER goes from 2,800 to almost 15,000 dollars/QALY. On the other hand, if the number of SoC dressings is 7, the PRP choice becomes cost-saving (ICER = - 10,011.82).
2. The total procedure costs for PRP range from a minimum of 733 to a maximum of 1,100. If the total procedure costs for PRP were equal to 1,100 instead of the base case, the ICER from 2,800 goes to 9,766 dollars/QALY. On the other hand, if the procedure cost is 733, the PRP choice becomes cost-saving (ICER = - 4,163).
3. The number of PRP medications ranges from a minimum of 1 to a maximum of 4. If the number of medications for PRP equals 4 instead of the base case, the ICER from 2,800 goes to 13,655 dollars/QALY. On the other hand, if the procedure cost is 1, the PRP choice becomes equal to the base case scenario (ICER = 2,800).
4. The SoC preparation time ranges from a minimum of 10 to a maximum of 20. If the preparation time is 10 instead of the base case 20, the ICER goes from 2,800 to almost 12,562 dollars/QALY.
5. The Regen KIT's price ranges from a minimum of $750 to a maximum of $990. If the PRP kit was priced at $990 instead of the base case, the ICER from 2,800 goes to 7,360 dollars/QALY, remaining cost-effective. On the other hand, if the price was 750, the PRP choice becomes cost-saving (ICER = - 1,756).

A Threshold analysis was carried out to define the price level at which PRP would be cost-saving. Regarding the first research question, it emerged that PRP became cost-saving in the first year after the fifth medication. About the second question, it was found that when the price of the regen kit is below $797, it becomes a cost-saving strategy.

A threshold analysis was also performed to determine the number of weekly medications needed for the Soc and the PRP. In detail, a two-way sensitivity analysis was performed. We find out that the number of PRP and Soc medications per week affects the final results. Starting from the two extremes, when PRP has its base case scenario of one per week complete medication and the Soc medication is three, the ICER goes up to around 15,000 $/QALY. Enhancing the number of PRP full medications increases the ICER. For example, if PRR would need four complete medications per week and Soc the base case (five), the ICER would be 13,655 $/QALY. Keeping the four full medications for the PRP strategy and lowering the medication to three per week would have an ICER of around 26,000 $/QALY. The definition of the PRP as the cost-effectiveness strategy is based on robust data but can be reduced by different elements, such as the number of medications for the two strategies.

Finally, a Monte Carlo simulation was employed to conduct a comprehensive probabilistic sensitivity analysis. This simulation methodically explored a vast array of possible scenarios, totaling 10,000. This approach allowed for a thorough exploration of the factors that could influence the outcome of the analysis, providing a more complete and nuanced understanding of the situation at hand. The model's parameters and variables vary based on the assigned distribution. Table 6 shows the results of corresponding acceptability curve with WTP thresholds. For each WTP threshold, the percentage of cases favoring PRP or HA is displayed, where the percentage of convenient iterations is derived from the Monte Carlo simulation. For instance, at $12,000/QALY, PRP treatment has an 87% probability of being convenient, while at $18,000/QALY, the probability is almost 100%.

Conclusion

This study conducts a comparative analysis of the cost-effectiveness of platelet-rich plasma (PRP) therapy versus standard care for treating diabetic foot ulcers (DFU) in high orthopedic risk patients, specifically those with grade 3A ulcers, according to the University of Texas (UT) classification. The study employs a micro-costing method, which allows for a detailed assessment of each treatment's direct and indirect costs. The data is based on a conservative meta-

Table 6 CE Acceptability Curve Results

Weight	Strategy	Strategy Name	Acceptability (%)
0	0	PRP	0.35
0	1	Soc	0.65
6000	0	PRP	0.63
6000	1	Soc	0.36
12,000	0	PRP	0.87
12,000	1	Soc	0.12
18,000	0	PRP	0.97
18,000	1	Soc	0.02
24,000	0	PRP	0.99
24,000	1	Soc	0.002
30,000	0	PRP	1
30,000	1	Soc	0
36,000	0	PRP	1
36,000	1	Soc	0
42,000	0	PRP	1
42,000	1	Soc	0
48,000	0	PRP	1
48,000	1	Soc	0
54,000	0	PRP	1
54,000	1	Soc	0
60,000	0	PRP	1
60,000	1	Soc	0
66,000	0	PRP	1
66,000	1	Soc	0
72,000	0	PRP	1
72,000	1	Soc	0
78,000	0	PRP	1
78,000	1	Soc	0

analysis, ensuring the comparison is grounded in reliable clinical evidence. Some conclusions that have been drawn lead to beneficial considerations regarding the following issues:

1. Economic Efficiency: Although PRP therapy has a higher initial cost, it requires fewer interventions and additional treatments than standard care.

2. Reduced Resource Utilization: given that PRP therapy may decrease the need for dressings, hospitalizations, and other medical procedures, leading to lower healthcare costs within the first year of treatment.

3. Clinical Benefits: PRP has the potential to promote faster and more sustained healing, which can reduce long-term complications and improve the patient's quality of life.

Despite the higher upfront cost, the potential of PRP therapy to minimize additional interventions supports its economic viability, making it a promising alternative for managing advanced diabetic foot ulcers. This study and others that have compared PRP practices indicate that PRP procedures can be fundamental in treating specific health conditions. These conditions impact the aging process and improve the patient's overall health, resulting in better performance.

Ethical Statement

This study does not contain human/animal test subjects.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Disclosure

The authors report no conflicts of interest in this work.

References

1. Rayner R, Carville K, Keaton J, et al. Leg ulcers: atypical presentations and associated co-morbidities. *Wound Pract Res*. 2009;17(4):168–185.
2. Agale SV. Chronic leg ulcers: epidemiology, aetiopathogenesis, and management. *Ulcers*. 2013;2013(1):ArticleID413604:9. doi:10.1155/2013/413604
3. Gould L, Abadir P, Brem H, et al. Chronic wound repair and healing in older adults: current status and future research. *Wound Repair Regen*. 2015;23(1):1–13. doi:10.1111/wrr12245
4. Linertová R, Del Pino-Sedeño T, G PL, et al. Cost-effectiveness of platelet-rich plasma for diabetic foot ulcer in Spain. *Int J Low Extrem Wounds*. 2021;20(2):119–127.
5. Zhang P, Lu J, Jing Y, Tang S, Zhu D, Bi Y. Global epidemiology of diabetic foot ulceration: a systematic review and meta-analysis. *Ann Med*. 2017;49(2):106–116. doi:10.1080/07853890.2016.1231932
6. Carter Marissa J, DaVanzo J, Haught R, et al. Chronic wound prevalence and the associated cost of treatment in medicare beneficiaries: changes between 2014 and 2019. *J Med Eco*. 2023;26(1):894–901. doi:10.1080/13696998.2023.2232256
7. R NS, J CM, E FC, et al. An economic evaluation of the impact, cost, and medicare policy implications of chronic nonhealing wounds. *Value Health*. 2018;21(1):27–32. doi:10.1016/j.jval.2017.07.007
8. Nussbaum SR, Carter MJ, Fife CE, et al. An economic evaluation of the impact, cost, and medicare policy implications of chronic nonhealing wounds. *Value in Health*. 2018;21(1):27–32.
9. Margolis DJ, Allen-Taylor L, Hoffstad O, Berlin JA. Diabetic neuropathic foot ulcers and amputation. *Wound Repair Regen*. 2005;13(3):230–236.
10. Greer N, Foman N, Dorrian J, et al. Advanced wound care therapies for nonhealing diabetic, venous, and arterial ulcers: a systematic review. *VAESP Project*. 2012.
11. Buckley CM, O'Farrell A, Canavan RJ, et al. Trends in the incidence of lower extremity amputations in people with and without diabetes over a five-year period in the Republic of Ireland. *PLoS One*. 2012;7(7):e41492. doi:10.1371/journalpone0041492
12. Brem H, Tomic-Canic M. Cellular and molecular basis of wound healing in diabetes. *J Clin Invest*. 2007;117(5):1219–1222. doi:10.1172/JCI32169
13. Armstrong DG, Tan TW, Boulton AJ, et al. Diabetic foot ulcers: a review. *JAMA*. 2023;330(1):62–75. doi:10.1001/jama.2023.10578
14. Creager MA, Matsushita K, Arya S, Beckman JA, Duval S, Goodney PP. American heart association advocacy coordinating committee, reducing nontraumatic lower-extremity amputations by 20% by 2030: time to get to our feet: a policy statement from the American Heart Association. *Circulation*. 2021;143(17):e875–e891. doi:10.1161/CIR.0000000000000967
15. Hicks CW, Selvarajah S, Mathioudakis N, et al. Burden of infected diabetic foot ulcers on hospital admissions and costs. *Ann Vasc Surg*. 2016;33:149–158. doi:10.1016/javsg201511025
16. Boulton AJ, Vileikyte L, Ragnarson-Tennvall G, Apelqvist J. The global burden of diabetic foot disease. *Lancet*. 2005;366(9498):1719–1724. doi:10.1016/S0140-6736(05)67698-2
17. Tennvall GR, Apelqvist J. Health-economic consequences of diabetic foot lesions. *Clin Infect Dis*. 2004;39(Suppl, 2):S132–S139. doi:10.1086/383275
18. Rice JB, Desai U, Cummings AK, et al. Burden of DFUs for medicare and private insurers. *Diabetes Care*. 2014;37(3):651–658. doi:10.2337/dc13-2176

19. Stockl K, Vanderplas A, Tafesse E, Chang E. Costs of lower-extremity ulcers among patients with diabetes. *Diabetes Care*. 2004;27(9):2129–2134. doi:10.2337/diacare.27.9.2129
20. Siersma V, Thorsen H, Holstein PE, et al. Importance of factors determining the low health-related quality of life in people presenting with a diabetic foot ulcer: the Eurodiale study. *Diabet Med*. 2013;30(1382):1382–1387. doi:10.1111/dme12254
21. Hopkins RB, Burke N, Harlock J, et al. Economic burden of illness associated with diabetic foot ulcers in Canada. *BMC Health Serv Res*. 2015;15 (13). doi:10.1186/s12913-015-0687-5
22. Bonaldi C, Romon I, Fago-Campagna A. Impacts of population aging and obesity on the evolution of the prevalence of treated diabetes: situation in metropolitan France by 2016. *Bull Epidemiol Hebd*. 2006;(10):69–76.
23. Jeffcoate W, Bakker K. World diabetes day: footing the bill. *Lancet*. 2005;365(9470):1527. doi:10.1016/S0140-6736(05)66437-9
24. Picard F, Hersant B, Bosc R, P MJ. The growing evidence for the use of platelet-rich plasma on diabetic chronic wounds: a review and a proposal for a new standard care. *Wound Repair Regener*. 2015;23(5):638–643. doi:10.1111/wrr.12317
25. Andia I, Abate M. Platelet-rich plasma: underlying biology and clinical correlates. *Regener Med*. 2013;8(5):645–658. doi:10.2217/rme.13.59
26. Scimeca CL, Bharara M, Fisher TK, et al. Novel use of platelet-rich plasma to augment curative diabetic foot surgery. *J Diabetes Sci Technol*. 2010;4(5):1121e6. doi:10.1177/193229681000400510
27. Mazzucco L, Medici D, Serra M, et al. The use of autologous platelet gel to treat difficult-to-heal wounds: a pilot study. *Transfusion*. 2004;44 (7):1013–1018. doi:10.1111/j.1537-2995.2004.03366.x
28. Saad Setta H, Elshahat A, Elsherbiny K, Massoud K, Safe I. Platelet-rich plasma versus platelet-poor plasma in the management of chronic diabetic foot ulcers: a comparative study. *Int Wound J*. 2011;8(3):307–312. doi:10.1111/j.1742-481X.2011.00797.x
29. O'Meara SM, Cullum NA, Majid M, Sheldon TA. Systematic review of antimicrobial agents used for chronic wounds. *Br J Surg*. 2001;88(1):4–21. doi:10.1046/j.1365-2168.2001.01631.x
30. Kantor J, Margolis DJ. Treatment options for diabetic neuropathic foot ulcers: a cost-effectiveness analysis. *Dermatol Surg*. 2001;27(4):347–351. doi:10.1046/j.1524-4725.2001.00280.x
31. Suthar M, Gupta S, Bukhari S, Ponemone V. Treatment of chronic non-healing ulcers using autologous platelet rich plasma: a case series. *J Biomed Sci*. 2017;24(16). doi:10.1186/s12929-017-0324-1
32. Lacci KM, Dardik A. Platelet-rich plasma: support for its use in wound healing Yale. *J Biol Med*. 2010;83:,1–9.
33. Ahmed M, A RS, Hassan A, Eskander F. Platelet-rich plasma for the treatment of clean diabetic foot ulcers. *Ann Vasc Surg*. 2017;38:206–211. doi:10.1016/j.avsg.2016.04.023
34. Dasari N, Jiang A, Skochdopole A, et al. Updates in diabetic wound healing. *Inflam Scar Semin Plast Surg*. 2021;35(3):,153–158. doi:10.1055/s-0041-1731460
35. R DV, Hanft J, P FC, M BJ. A prospective, randomized, controlled trial of autologous platelet-rich plasma gel for the treatment of diabetic foot ulcers. *Ostomy Wound Manage*. 2006;52(6):68.
36. Peng Y, Wang J, Liu X, et al. Efficacy of platelet-rich plasma in the treatment of diabetic foot ulcers: a systematic review and meta-analysis. *Ann Vasc Surg*. 2024;98:365–373. doi:10.1016/j.avsg.2023.05.045
37. Guerid S, Darwiche S, E BMM, A AL, Benathan M, Raffoul W. Autologous keratinocyte suspension in platelet concentrate accelerates and enhances wound healing—A prospective randomized clinical trial on skin graft donor sites: platelet concentrate and keratinocytes on donor sites, Fibrogen. *Tissue Rep*. 2013;6:1–8.
38. Conde-Montero E, de la Cueva Dobao P, Martínez González JM. Platelet-rich plasma for the treatment of chronic wounds: evidence to date. *Chronic Wound Care Manag Res*. 2017;4:107–120. doi:10.2147/CWCMRS118655
39. Hirase T, Ruff E, Surani S, Ratnani I. Topical application of platelet-rich plasma for diabetic foot ulcers: a systematic review. *World J Diabetes*. 2018;9(10):172–179. doi:10.4239/wjd.v9.i10.172
40. Del Pino-Sedeño T, Trujillo-Martín MM, Andia I, et al. Platelet-rich plasma for the treatment of diabetic foot ulcers: a meta-analysis. *Wound Repair Regen*. 2019;27(2):170–182. doi:10.1111/wrr.12690
41. Hsieh TS, Chiu WK, Yang TF, Wang HJ, Chen C. A meta-analysis of the evidence for assisted therapy with platelet-rich plasma for atrophic acne scars. *Aesthetic Plast Surg*. 2019;43(6):1615–1623. doi:10.1007/s00266-019-01471-w
42. Shen Z, Zheng S, Chen G, et al. Efficacy and safety of platelet-rich plasma in treating cutaneous ulceration: a meta-analysis of rando-mized controlled trials. *J Cosmet Dermatol*. 2019;18(2):495–507. doi:10.1111/jocd.12853
43. Ding H, Fu XL, Miao WW, Mao XC, Zhan MQ, Chen HL. Efficacy of autologous platelet-rich gel for diabetic foot wound healing: a meta-analysis of 15 randomized controlled trials. *Adv Wound Care*. 2019;8(5):195–207. doi:10.1089/wound.2018.0861
44. Li Y, Gao Y, Gao Y, et al. Autologous platelet-rich gel treatment for diabetic chronic cutaneous ulcers: a meta-analysis of randomized controlled trials. *J Diabetes*. 2019;11(5):359–369. doi:10.1111/1753-0407.12850
45. Xia Y, Zhao J, Xie J, Lv Y, Cao DS. The efficacy of platelet-rich plasma dressing for chronic nonhealing ulcers: a meta-analysis of 15 randomized controlled trials. *Plast Reconstr Surg*. 2019;144(6):1463–1474. doi:10.1097/PRS.0000000000006281
46. Hu Z, Qu S, Zhang J, et al. Efficacy and safety of platelet-rich plasma for patients with diabetic ulcers: a systematic review and meta-analysis. *Adv Wound Care*. 2019;8(7):298–308. doi:10.1089/wound.2018.0842
47. Gentile P, Garcovich S. Systematic review: adipose-derived mesenchymal stem cells, platelet-rich plasma and biomaterials as new regenerative strategies in chronic skin wounds and soft tissue defects. *Int J Mol Sci*. 2021;22(4):1538. doi:10.3390/ijms22041538
48. OuYang H, Tang Y, Yang F, et al. Platelet-rich plasma for the treatment of diabetic foot ulcer: a systematic review. *Front Endocrinol*. 2023;14. doi:10.3389/fendo.2023.1256081
49. Syafira F, B IM, Sriwulandari R. Platelet-rich plasma (prp) as therapy for diabetic foot ulcer (dfu): a systematic review and meta-analysis of the latest randomized controlled trials. *Diabetes Epidemiol Manage*. 2023;100178.
50. Deng J, Yang M, Zhang X, Zhang H. Efficacy and safety of autologous platelet-rich plasma for diabetic foot ulcer healing: a systematic review and meta-analysis of randomized controlled trials. *J Orthopaedic Surg Res*. 2023;18(1):370. doi:10.1186/s13018-023-03854-x
51. Dougherty EJ. An evidence-based model comparing the cost-effectiveness of platelet-rich plasma gel to alternative therapies for patients with nonhealing diabetic foot ulcers. *Adv Skin Wound Care*. 2008;21(12):568–575. doi:10.1097/01.ASW.0000323589.27605.71
52. C CR, P DN, A BF. Platelet-rich plasma in skin ulcer treatment. *Wounds*. 2013;25(9):256–262.

53. Linertová R, Del Pino-Sedeño T, Pérez LG, et al. Cost-effectiveness of platelet-rich plasma for diabetic foot ulcer in Spain [published online ahead of print, 2020 Feb 10]. *Int J Low Extrem Wounds*. 2020:1534734620903239. doi:10.1177/1534734620903239.
54. Russo S, Landi S, Courric S. Cost-effectiveness analysis for the treatment of diabetic foot ulcer in France: platelet-rich plasma vs standard of care. *Clinicoecon Outcomes Res*. 2022;14:1–10. doi:10.2147/CEORS327191
55. Sylvaine C, Denizot C, Albache N, Robu E, Labbe L, Agopian H. Autologous platelet gel: an help in chronic deep diabetic foot ulcers treatment in "2019 diabetic foot conference abstracts". *J Diabetes Sci Technol*. 2020;14(3):601–678. doi:10.1177/1932296819897643
56. Briggs A, Claxton K, Sculpher M. *Decision Modelling for Health Economic Evaluation*. Oxford: Oxford University Press; 2006.
57. Nilsson A, Willis M, Neslusan C. A review of the costs of lower limb amputations in patients with diabetes in the US. *Value Health*. 2018;21:S73. doi:10.1016/j.jval.2018.04.492
58. Margolis DJ, Malay DS, Hoffstad OJ, et al. Economic burden of diabetic foot ulcers and amputations: data points #3, 2011 Mar 8. In: *Data Points Publication Series [Internet]*. Rockville (MD): Agency for Healthcare Research and Quality (US); 2011.
59. Van Hout B, Janssen MF, Feng YS, et al. Interim scoring for the EQ-5D-5L: mapping the EQ-5D-5L to EQ-5D-3L value sets. *Value Health*. 2012;15(5):708–715. doi:10.1016/j.jval.2012.02.008
60. Redekop WK, Stolk EA, Kok E, Lovas K, Kalo Z, Busschbach JJV. Diabetic foot ulcers and amputations: estimates of health utility for use in cost-effectiveness analyses of new treatments. *Diabetes Metab*. 2004;30(6):549–556. doi:10.1016/S1262-3636(07)70154-4
61. Moulik PK, Mtonga R, Gill GV. Amputation and mortality in new-onset diabetic foot ulcers stratified by etiology. *Diabetes Care*. 2003;26 (2):491–494. doi:10.2337/diacare.26.2.491
62. Dubský M, Jirkovská A, Bem R, et al. Risk factors for recurrence of diabetic foot ulcers: prospective follow-up analysis in the Eurodiale subgroup. *Int Wound J*. 2013;10(5):555–561. doi:10.1111/j.1742-481X.2012.01022.x
63. Briggs AH, Goeree R, Blackhouse G, O'Brien BJ Probabilistic analysis of cost-effectiveness models: choosing between treatment strategies for gastroesophageal reflux disease. *Med Decis Mak*. 2002;22(4):290–308.