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Longitudinal changes in humoral immune markers after tibial transverse transport in patients with type 2 diabetes-related foot ulcers: a retrospective study using generalized estimating equations

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Research Article

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Longitudinal changes in humoral immune markers after tibial transverse transport in patients with type 2 diabetes-related foot ulcers: a retrospective study using generalized estimating equations

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Abstract

Background: The dynamics of circulating humoral immune markers after tibial transverse transport (TTT) and their association with diabetic foot ulcer healing remain incompletely understood. This study examined serial changes in eight immune markers according to six-month wound outcomes.

Methods: This single-center retrospective study included 66 patients with type 2 diabetes and Wagner grade 3–4 foot ulcers who underwent TTT between May 2022 and August 2023. Patients were classified as healed (n = 54) or unhealed (n = 12) at six months. Serum immunoglobulin G (IgG), A (IgA), M (IgM), E (IgE), complement C3 and C4, and immunoglobulin κ and λ light chains were assessed before surgery and on postoperative days 3, 7, 14, 21 and 36. Within-group temporal patterns were evaluated using Friedman tests; group-by-time associations were examined using generalized estimating equations.

Results: Wound healing was reported in 54/66 patients (81.8%); mean healing time was 82.4 ± 15.7 days. Among the 12 patients classified as unhealed, three underwent amputation, six died and three had persistent wounds. Group-by-time interactions were reported for IgG (Wald $\chi^2 = 13.82$, $P = 0.013$), IgM ($\chi^2 = 12.95$, $P = 0.031$) and λ light chain ($\chi^2 = 15.68$, $P < 0.01$). From day 14, IgG and λ light-chain levels were lower in the healed group at selected postoperative assessments. No significant group-by-time interactions were reported for IgA, IgE, C3, C4 or κ light chain.

Conclusions: Serial IgG and λ light-chain measurements differed by healing status after TTT in this retrospective cohort. These associations are hypothesis-generating; prospective validation and adjustment for infection severity, perfusion and other confounding factors are required before clinical prognostic use.

Keywords: Diabetic foot ulcer; Tibial transverse transport; Humoral immunity; Immunoglobulins; Generalized estimating equations; Wound healing

Background

Diabetes-related foot ulcers are serious complications associated with infection, limb ischemia, impaired mobility and mortality [1–7]. Managing advanced ulcers remains challenging despite comprehensive wound care, infection treatment and vascular assessment. Tibial transverse transport (TTT), a limb-preserving procedure based on the Ilizarov tension–stress principle, has been studied as a means of promoting microvascular remodeling and tissue repair [8–13].

Innate and adaptive immune responses contribute to wound inflammation and resolution. Circulating immunoglobulins and complement proteins may vary with infection, metabolic state and tissue injury [14–18]. Previous TTT investigations have addressed vascular mechanisms and inflammatory responses [19–22]. Reports concerning immunoglobulin profiles are relatively limited [23–25], and it is unclear whether the trajectories of these markers differ according to later wound-healing outcomes.

We therefore described perioperative changes in IgG, IgA, IgM, IgE, C3, C4, κ light chain (KAP) and λ light chain (LAM) in patients undergoing TTT and compared their longitudinal patterns between patients classified by six-month wound outcomes. This observational study was not designed to establish immunological mechanisms or treatment efficacy versus alternative interventions.

Methods

Study design and population. We retrospectively reviewed 66 patients who underwent tibial transverse transport for type 2 diabetes-related foot ulcers at Mianyang Central Hospital between May 2022 and August 2023. Eligible patients had type 2 diabetes diagnosed according to accepted clinical criteria [26] and Wagner

grade 3–4 foot ulcers classified using established diabetic foot grading definitions [27]. All procedures were performed by the same orthopedic team. The clinical records and six-month outcomes were reviewed retrospectively.

Ethical oversight. The Biomedical Ethics Committee of Mianyang Central Hospital approved the study protocol (approval number S20240201-01; approval date: 19 January 2024). The study was conducted in accordance with the Declaration of Helsinki.

Intervention and perioperative care. The procedure involved a tibial cortical window measuring approximately 60 × 20 mm, external fixation and transverse transport after wound debridement. Transport began on postoperative day 7 at 1 mm/day (divided into six adjustments) and was reversed on days 14–20 at the same rate. The transport device was removed around postoperative day 35. Standard care included glycemic management, assessment of infection and perfusion, wound dressings, and individualized supportive treatment [28–31].

Laboratory sampling. Venous blood was collected on the day before surgery and on postoperative days 3, 7, 14, 21 and 36. Serum was separated by centrifugation and stored at −80 °C before measurement. The study records describe determination of IgG, IgA, IgM, IgE, C3, C4, KAP and LAM using a BD FACSCanto II platform. The assay details should be interpreted in the context of the laboratory protocol.

Outcomes. At six months, healing was defined as at least 90% wound-area closure without conspicuous exudate, with fresh granulation, no tenderness and no further dressing requirement. The categories were healed versus unhealed; amputation, death and persistent ulceration were reported as adverse outcomes. This operational definition differs from complete epithelialization and should be retained explicitly when interpreting the findings.

Statistical analysis. Analyses were performed using R version 4.2.1 and IBM SPSS version 20.0. Continuous immune-marker variables were summarized using medians and interquartile ranges. Mann–Whitney U tests were used for baseline comparisons and Friedman tests for within-group overall time effects. Generalized estimating equations (GEE) were used to assess time, group and group-by-time effects. Missing data were described as having been handled by multiple imputation by chained equations. Time-specific comparisons

are reported as provided by the study analysis, without interpreting omnibus Friedman tests as evidence of individual pairwise differences. Statistical significance was assessed at $P < 0.05$. The missing-data approach was based on multiple-imputation methodology [32], and the longitudinal GEE framework followed established methods for correlated observations [33].

Results

Participant characteristics and clinical outcomes. The cohort comprised 66 patients (48 men and 18 women); 54 were classified as healed (41 men and 13 women) and 12 as unhealed (7 men and 5 women). Clinical outcomes were evaluated over six months. Baseline characteristics are presented in Table 1 (insert Table 1 here).

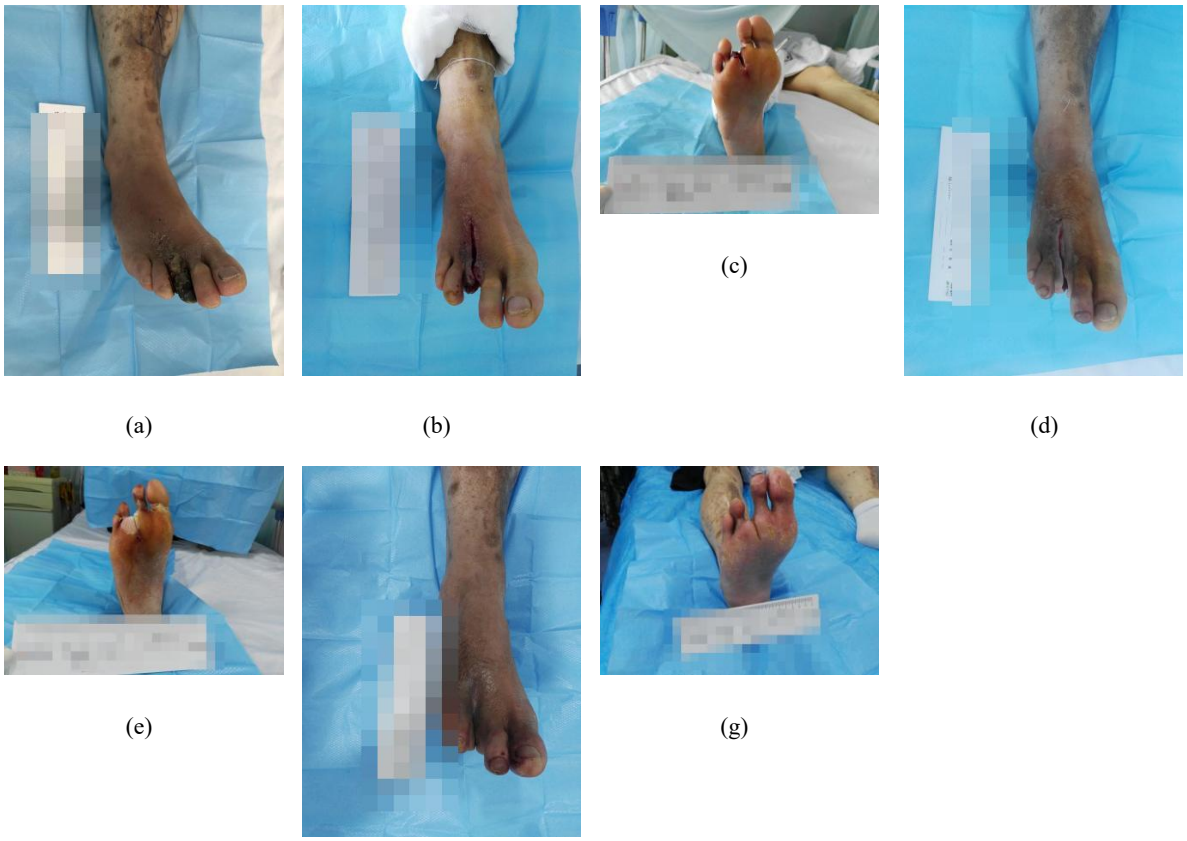
Table 1. Baseline clinical characteristics

Characteristic	Healed (n = 54)	Unhealed (n = 12)	t / χ^2	P value
Sex (male/female), n	41/13	7/5	1.532	0.216
Age (years), mean ± SD	65.2±9.7	67.5±10.5	0.696	0.496
Diabetes duration (years), mean ± SD	10.1±3.8	10.7±4.5	0.429	0.674
Wagner grade (3/4), n	38/16	8/4	0.064	0.801

Values are presented as reported in the study dataset; IQR, interquartile range; CI, confidence interval. Statistical contrasts refer to the tests specified in Methods.

The mean healing time was 82.4 ± 15.7 days. Among 12 patients not classified as healed, three underwent amputation, six died within 1–4 months after surgery, and three had persistent wounds. Death is a competing event for the healing outcome and is reported separately from persistent ulceration. Pin-tract infection was recorded in one healed and three unhealed patients, wound infection in two unhealed patients, and deep vein thrombosis in one unhealed patient. Representative clinical photographs demonstrating the wound course are shown in Fig. 2 (insert Fig. 2 here).

Figure 2. Representative clinical photographs of a 57-year-old male patient with a Wagner grade 4 diabetes-related foot ulcer at sequential stages of perioperative care and follow-up. Seven panels (a–g) depict clinical wound appearances.



(a) (b) (c) (d)

(e) (f) (g)

Preoperative immune profiles. No statistically significant baseline differences were reported for the eight measured immune markers using Mann–Whitney U tests (all $P > 0.05$; Table 2). Lack of statistical significance should not be interpreted as proof of baseline equivalence, especially with only 12 patients in the unhealed group.

Table 2. Baseline immune markers

Marker	Healed	Unhealed	Z	P value
IgG (g/L)	11.80(9.74,16.75)	13.5(11.1,16.25)	-0.681	0.500
IgA (g/L)	2.99(2.01, 4.19)	3.2(2.40,4.03)	-0.654	0.518
IgM (g/L)	0.83(0.52,1.23)	0.85(0.65,1.29)	-0.626	0.535
IgE (IU/mL)	38.55(20.25,192.75)	70.95(36.75,206)	-0.966	0.338
C3 (g/L)	1.16(1.04,1.36)	1.26(1.07,1.42)	-0.578	0.568
C4 (g/L)	0.33(0.28,0.37)	0.36(0.28,0.45)	-0.852	0.398
KAP (g/L)	2.67(2.37,4.1)	3.23(2.57,3.89)	-0.826	0.413
LAM (g/L)	1.68(1.50,2.37)	1.84(1.61,2.37)	-0.792	0.433

Values are presented as reported in the study dataset; IQR, interquartile range; CI, confidence interval. Statistical contrasts refer to the tests specified in Methods.

Within-group changes. In the healed group, Friedman tests indicated overall time effects for IgG, IgA, IgE, C3, C4, KAP and LAM but not IgM. In the unhealed group, overall time effects were observed for all markers except IgA (Tables 3 and 4). These omnibus results describe overall longitudinal variation and do not establish the significance of individual adjacent time-point differences.

Table 3. Serial immune markers in the healed group

Marker	Day −1	Day 3	Day 7	Day 14	Day 21	Day 36	χ^2	P value
IgG (g/L)	11.80(9.74, 16.75)	11.20(9.08, 15.55)*	11.30(9.16, 15.75)	11.30(10.20, 15.05)	11.70(9.73, 15.40)	11.70(10.50, 14.40)	13.94	0.016
IgA(g/L)	2.99(2.01, 4.19)	2.50(1.85, 3.65)*	2.39(1.93, 3.46)*	2.40(1.89, 3.61)*	2.52(1.87, 3.25)*	2.51(1.75, 3.53)**	22.71	<0.001
IgM(g/L)	0.83(0.52, 1.23)	0.69(0.45, 1.09)	0.75(0.49, 1.19)	0.79(0.51, 1.20)	0.72(0.54, 1.24)	0.76(0.59, 1.06)	8.25	0.143
IgE(IU/mL)	38.55(20.25, 192.75)	49.55(21.08, 201.50)	41.20(23.88, 173.25)	38.40(20.92, 147.25)	37.90(20.25, 202.50)	29.80(23.25, 163.00)	17.19	0.004
C3 (g/L)	1.16(1.04, 1.36)	1.20(1.08, 1.41)*	1.27(1.20, 1.47)	1.37(1.18, 1.49)*	1.26(1.08, 1.42)	1.23(1.02, 1.39)	15.99	0.007
C4 (g/L)	0.33(0.28, 0.37)	0.33(0.26, 0.38)	0.37(0.29, 0.41)	0.38(0.32, 0.42)*	0.35(0.30, 0.42)	0.36(0.30, 0.39)	19.58	<0.001
KAP(g/L)	2.67(2.37, 4.10)	2.66(2.25, 3.43)*	2.61(2.23, 3.59)*	2.60(2.35, 3.63)	2.69(2.23, 3.71)	2.70(2.44, 3.51)	17.32	0.004
LAM(g/L)	1.68(1.50, 2.37)	1.71(1.38, 1.98)*	1.79(1.39, 1.92)	1.61(1.44, 1.85)	1.59(1.49, 1.93)	1.71(1.48, 1.97)	13.51	0.019

Values are presented as reported in the study dataset; IQR, interquartile range; CI, confidence interval. Statistical contrasts refer to the tests specified in Methods.

Table 4. Serial immune markers in the unhealed group

Marker	Day −1	Day 3	Day 7	Day 14	Day 21	Day 36	χ^2	P value
IgG(g/L)	13.50(11.10, 16.25)	12.70(10.85, 15.80)	12.70(10.30, 15.25)	14.40(11.85, 17.70)	15.00(11.85, 17.20)	15.80(12.60, 17.40)	44.18	<0.001
IgA(g/L)	3.20(2.40, 4.03)	3.12(2.37, 3.93)	2.99(2.51, 3.53)	2.98(2.52, 3.75)	2.90(2.43, 3.67)	2.90(2.43, 3.67)	8.10	0.151
IgM(g/L)	0.85(0.65, 1.29)	0.80(0.64, 1.25)	0.76(0.61, 1.16)	0.87(0.65, 1.28)	0.88(0.66, 1.17)	0.96(0.71, 1.40)	17.51	0.004
IgE (IU/ml)	70.95(36.75, 206.00)	76.00(32.75, 212.75)	85.45(29.75, 170.75)	69.25(33.40, 149.25)	70.45(36.75, 139.25)	57.50(31.33, 150.75)	12.95	0.024
C3 (g/L)	1.26(1.07, 1.42)	1.20(1.03, 1.39)	1.30(1.09, 1.43)	1.36(1.19, 1.59)*	1.32(1.11, 1.48)	1.26(1.16, 1.48)	22.15	<0.001
C4 (g/L)	0.36(0.28, 0.45)	0.37(0.29, 0.45)	0.39(0.31, 0.47)	0.38(0.29, 0.45)	0.38(0.31, 0.43)	0.37(0.30, 0.43)	11.23	0.047
KAP(g/L)	3.23(2.57, 3.89)	3.03(2.52, 3.73)	2.99(2.44, 3.56)	3.29(2.72, 4.00)	3.33(2.76, 4.23)	3.64(2.92, 4.04)	37.70	<0.001
LAM(g/L)	1.84(1.61, 2.37)	1.78(1.45, 2.19)	1.78(1.45, 2.19)	1.85(1.53, 2.53)	1.99(1.59, 2.50)	2.01(1.77, 2.28)	24.32	<0.001

Values are presented as reported in the study dataset; IQR, interquartile range; CI, confidence interval. Statistical contrasts refer to the tests specified in Methods.

Longitudinal group comparisons. GEE analyses indicated time-by-group interactions for IgG (Wald χ^2 = 13.82, P = 0.013), IgM (Wald χ^2 = 12.95, P = 0.031) and λ light chain (Wald χ^2 = 15.68, P < 0.01; Table 5). No statistically significant interactions were observed for the other five measured markers. Time-specific group comparisons for these markers are summarized in Table 6 and interpreted as exploratory. The observed temporal trends for all eight markers are displayed in Fig. 1 (insert Fig. 1 here).

Table 5. Generalized estimating equation model effects

Marker	Time effect (Wald χ^2 / P)	Group effect (Wald χ^2 / P)	Time × group (Wald χ^2 / P)
IgG(g/L)	28.67/<0.001	1.25/0.264	13.82/0.013*
IgA(g/L)	26.54/<0.001	1.16/0.281	5.37/0.373
IgM(g/L)	17.51/0.004	0.89/0.345	12.95/0.031*
IgE(IU/ml)	7.31/0.199	0.99/0.321	4.61/0.470
C3(g/L)	29.66/<0.001	0.25/0.621	4.07/0.540
C4(g/L)	36.45/<0.001	0.34/0.560	3.35/0.650
KAP(g/L)	37.70/<0.001	1.42/0.233	9.27/0.098
LAM(g/L)	24.32/<0.001	2.89/0.090	15.68/<0.01*

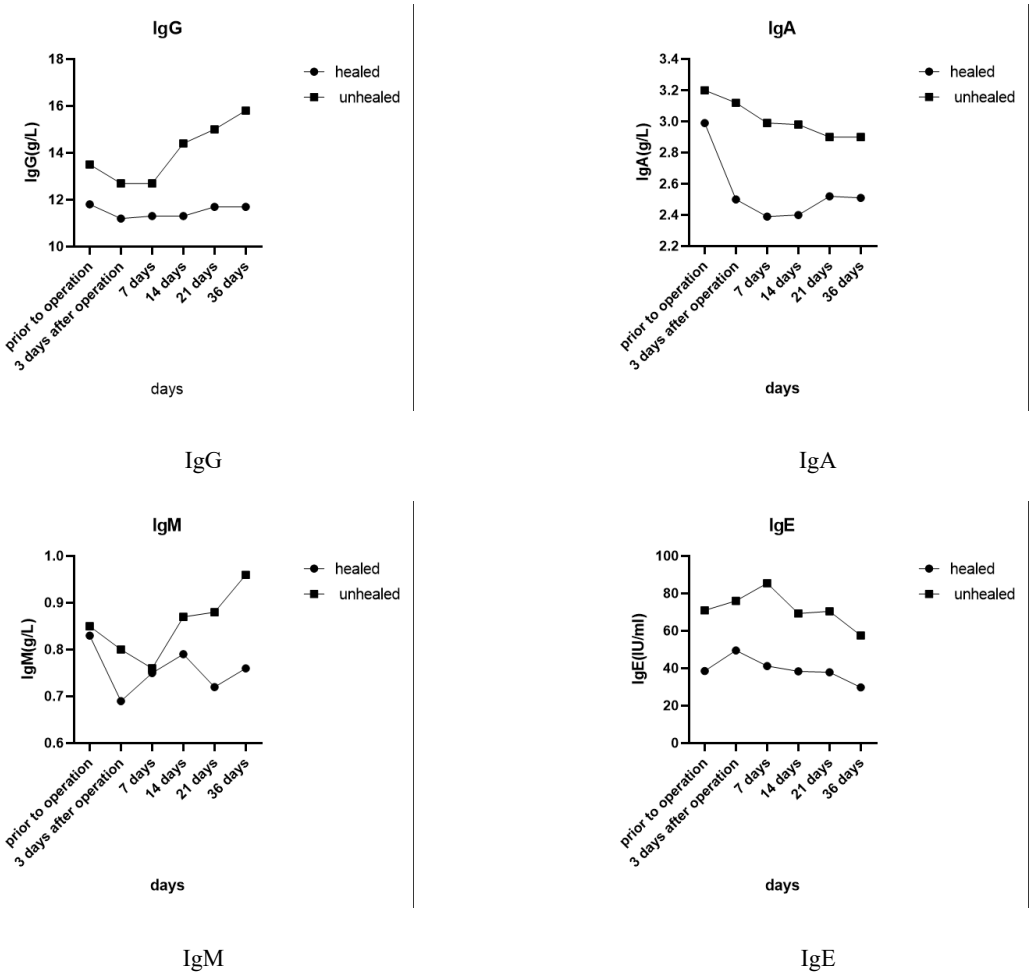
Values are presented as reported in the study dataset; IQR, interquartile range; CI, confidence interval. Statistical contrasts refer to the tests specified in Methods.

Table 6. Time-specific group contrasts from generalized estimating equations

Marker	Time	Healed median (IQR)	Unhealed median (IQR)	Difference (95% CI)	P value
IgG(g/L)	Day −1	11.80(9.74, 16.75)	13.50(11.10, 16.25)	-0.52(-3.10~2.07)	0.690
	Day 3	11.20(9.08, 15.55)	12.70(10.85, 15.80)	-1.58(-3.74~0.59)	0.150
	Day 7	11.30(9.16, 15.75)	12.70(10.30, 15.25)	-1.12(-3.26~1.01)	0.300
	Day 14	11.30(10.20, 15.05)	14.40(11.85, 17.70)	-2.27(-4.34~-0.20)	0.031*
	Day 21	11.70(9.73, 15.40)	15.00(11.85, 17.20)	-2.40(-4.50~-0.06)	0.044*
	Day 36	11.70(10.50, 14.40)	15.80(12.60, 17.40)	-2.80(-4.47~-1.14)	<0.001***
LAM(g/L)	Day −1	1.68(1.50, 2.37)	1.84(1.61, 2.37)	-0.15(-0.49~0.18)	0.365
	Day 3	1.71(1.38, 1.98)	1.78(1.45, 2.19)	-0.27(-0.56~0.01)	0.060
	Day 7	1.79(1.39, 1.92)	1.78(1.45, 2.19)	-0.14(-0.43~0.15)	0.350
	Day 14	1.61(1.44, 1.85)	1.85(1.53, 2.53)	-0.34(-0.63~-0.06)	0.018*
	Day 21	1.59(1.49, 1.93)	1.99(1.59, 2.50)	-0.35(-0.62~-0.08)	0.009*
	Day 36	1.71(1.48, 1.97)	2.01(1.77, 2.28)	-0.36(-0.57~-0.34)	0.001***
IgM (g/L)	Day −1	0.83(0.52,1.23)	0.85(0.65,1.29)	−0.028(-0.28~0.22)	0.824
	Day 3	0.69(0.45,1.09)	0.8(0.64,1.25)	−0.11(-0.33~0.11)	0.318
	Day 7	0.75(0.49,1.19)	0.76(0.61,1.16)	−0.05(-0.25~0.15)	0.643
	Day 14	0.79(0.51,1.20)	0.87(0.65,1.28)	−0.13(-0.34~0.10)	0.282
	Day 21	0.72(0.54,1.24)	0.88(0.66,1.17)	−0.08(-0.28~0.13)	0.451
	Day 36	0.76(0.59,1.06)	0.96(0.71,1.40)	−0.15(-0.36~0.07)	0.185

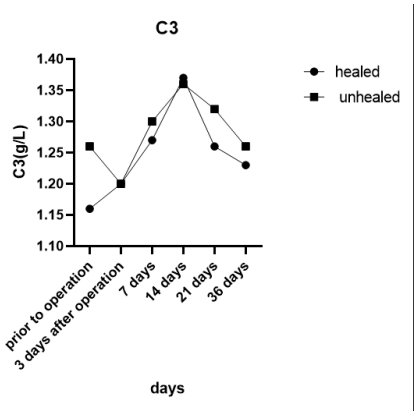
Values are presented as reported in the study dataset; IQR, interquartile range; CI, confidence interval. Statistical contrasts refer to the tests specified in Methods.

Figure 1. Longitudinal profiles of IgG, IgA, IgM, IgE, complement components C3 and C4, and immunoglobulin light chains κ (KAP) and λ (LAM) at the six study time points in healed and unhealed patients.

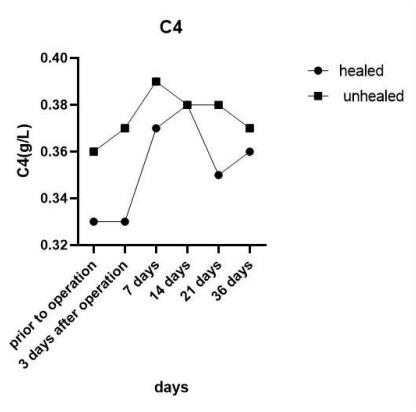


IgG IgA

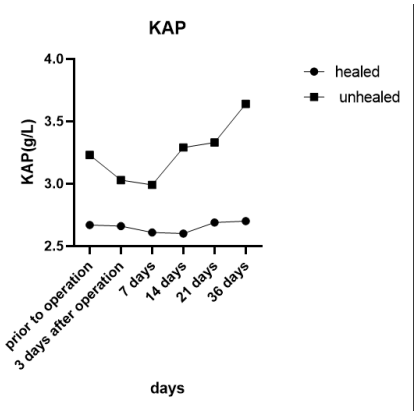
IgM IgE



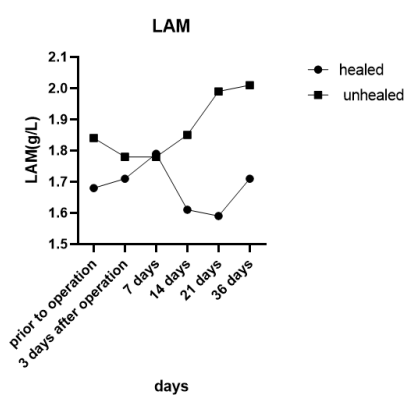
C3



C4



KAP



LAM

Discussion

The primary observation in this retrospective single-center cohort was that postoperative IgG and λ light-chain trajectories differed between the groups defined by the six-month outcome. Because the comparison is observational and infection, perfusion and glycemic control were not adequately adjusted for, a causal effect of TTT on immune responses or wound healing cannot be inferred. The contrast between healed and non-healed patients is also complicated by death as a competing event.

Previous studies have suggested vascular and inflammation-related biological effects of tibial cortical transport [8–13,19–22]. Immunoglobulin levels in diabetic foot disease may also be associated with infection and host characteristics [17,23]. The present clinical observations extend these questions to repeated postoperative sampling, but no untreated or alternative-treatment control group was available. Consequently, the reported healing proportion should not be used to infer comparative efficacy or a reduction in amputation risk caused

by TTT. In interpreting the biomarkers, general immunological roles of immunoglobulins and their light chains should be distinguished from causal mechanisms in the present cohort [34]. IgA contributes to mucosal immune defense [35], IgM participates in early and memory humoral responses [36], and IgE has established roles in allergic inflammation [37]. Elevated immunoglobulin light chains also arise in settings unrelated to wound repair, including plasma-cell disorders [38]; these references provide biological context rather than direct evidence for a TTT-mediated mechanism.

Omnibus longitudinal tests and time-specific contrasts address different hypotheses. Statistical significance for an overall Friedman or GEE interaction test was not taken as evidence that every individual time-point comparison was significant. Given the eight biomarkers and multiple comparisons, these findings should be regarded as exploratory.

The interpretation of healing outcomes is limited by six deaths among 12 participants classified as unhealed. The deaths occurred within 1–4 months of surgery, while immune measurements were scheduled through postoperative day 36. Death may affect completeness of follow-up and is a competing event for healing. Future analyses should examine this outcome separately and assess the influence of missing measurements.

Limitations include the small unhealed subgroup, retrospective design, absence of an alternative-treatment control group, potential selection bias, insufficient adjustment for infection, glycemic control, limb ischemia and revascularization, and six months of follow-up. Reporting of the laboratory methodology and time-specific sample completeness warrants further detail. Serum marker changes do not directly establish cellular immune mechanisms, and no validated prognostic thresholds can be proposed.

Conclusions

In this exploratory retrospective cohort, longitudinal IgG and λ light-chain profiles varied according to wound-healing classification after tibial transverse transport. These associations cannot establish causation or clinical predictive utility. Prospective external validation is needed before the markers are considered for routine clinical decision-making.

List of abbreviations

C3, complement component 3; C4, complement component 4; GEE, generalized estimating equations; IgA, immunoglobulin A; IgE, immunoglobulin E; IgG, immunoglobulin G; IgM, immunoglobulin M; KAP, κ light chain; LAM, λ light chain; TTT, tibial transverse transport.

Declarations

Ethics approval and consent to participate

This study was approved by the Biomedical Ethics Committee of Mianyang Central Hospital (approval number: S20240201-01; approval date: 19 January 2024). The study was conducted in accordance with the Declaration of Helsinki. Written informed consent to participate in the study was obtained from all 66 patients.

Consent for publication

Informed consent for publication of the clinical photographs was obtained from the patient(s) concerned.

Availability of data and materials

The datasets generated and/or analysed during the current study are not publicly available due to patient privacy and institutional requirements, but are available from the corresponding author on reasonable request, subject to any necessary institutional approvals and applicable data protection requirements.

Competing interests

The authors declare that they have no competing interests.

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This research received no external funding.

Authors' contributions

Zepeng Zhao contributed to conceptualization and study design, clinical data collection, statistical analysis, and manuscript drafting. Zhuojun Yi contributed to data analysis, critical review and editing, and supervision.

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Authors' information

Not applicable.

Clinical trial number

Not applicable.

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