# Return To Work After Cell Transplantation in Patients With Angiitis-Induced Critical Limb Ischemia and Factors Related

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**Research**

**Keywords:** Critical limb ischemia, cell transplantation, CD34+, return to work.

**Posted Date:** September 2nd, 2021

**DOI:** https://doi.org/10.21203/rs.3.rs-861401/v1

## Abstract

# Backgrounds:

Angiitis-induced critical limb ischemia (AICLI) patients, who are usually with young age and high amputation rate, always lose their labor force. Return to work (RTW), not only mean patients' physical health for they could undertake the work but also demonstrate their psychological well-being. While cell transplantation showed satisfactory efficacy for AICLI patients, few studies in terms of AICLI patients' returning to work after transplantation were reported.

# Methods

From May 2009 to May 2021, AICLI patients who underwent cell transplantation and completed a no less than 12-month follow-up were retrospectively enrolled. Primary endpoint was RTW. Patients' demographic characteristics, characteristics of ischemic limb, etc. were reviewed to analyze independent risk factors in terms of RTW.

# Results

171 AICLI patients (170 males) were enrolled with a mean age of 41.9 ± 9.6 years (range, 20–57 years). The 12-month and 24-month RTW cumulative rates were 69.4% (95% confidence interval [CI] 61.6%-75.6%) and 70.1% (95% CI 62.3%-76.2%), respectively. Age < 40 years (OR 2.659, 95% CI 1.138–6.719), and preoperative job as mental workers (OR 8.930, 95% CI 2.665–42.847) were identified as independent protective factors for RTW, perioperative limb infection of patients with ulcer or gangrene (OR 0.250, 95% CI 0.075–0.779) was identified as independent risk factor.

# Conclusion

AICLI patients who underwent cell transplantation were with a satisfactory mid-term RTW cumulative rate. AICLI patients < 40 years old with preoperative occupation as mental workers were more likely to return to work. Prevention of limb infection during the perioperative period is of great significance to RTW.

## 1. Introduction

Angiitis-induced critical limb ischemia (AICLI) patients, which is defined as ischemia caused by thromboangiitis obliterans (TAO) or other arteritis-related autoimmunological diseases such as systemic lupus erythematosus (SLE), psoriasis, Crohn's disease, etc., are usually with relatively young age and high amputation rate. Unfortunately, AICLI patients are usually with impaired or even depleted labor force due to the intolerable rest pain, ulcer or even gangrene, thus posing heavy burden to family and society.[1]

Nowadays, cell therapy has showed satisfactory results in treating AICLI,[2–5] and the ability to work after cell therapy is an important indicator of recovery for AICLI patients. Return to work, not only mean patients' physical health for they could undertake the work but also demonstrate their psychological well-being,[6,7] decreases the financial burden on patients, their families and society.[8] On the other hand, failure to return to work might increase patients' incidence of depression and impair their quality of life.[9–11]

To the best of our knowledge, no previous studies in terms of returning to work after intervention for patients with AICLI were reported. As one with relatively large series of AICLI patients in China, our center initialed the cell therapy (peripheral blood mononuclear cells [PBMNCs] and purified $CD34^+$ cells [PCCs] transplantation) for AICLI patients in 2009 and have accumulated valuable experiences since then.[2,4,5,12] In order to report the outcomes of AICLI patients' return to work after cell therapy and further identify the factors associated to failure to return to work, we retrospectively reviewed and analyzed the data of over 190 AICLI patients during the past 11 years.

## 2. Materials And Methods

# 2.1. Patients and Data Collection

This study was approved by the Committee for the Protection of Human Subjects at Zhongshan Hospital, Fudan University. Written informed consent was obtained from each patient included in the study. It was performed in agreement with the ethical principles of the Declaration of Helsinki.

A consecutive cohort from May 2009 to May 2021 was retrospectively enrolled in our center and included 192 AICLI patients who received PBMNCs or PCCs transplantation. The inclusion and exclusion criteria for cell transplantation were described previously [4]. Briefly, male or female aged between 18 and 80 years with AICLI (Rutherford classification [RC] 4–5) which was confirmed by clinical manifestation and computed tomographic angiography (CTA), magnetic resonance angiography (MRA), or digital subtraction angiography (DSA) was included. And the exclusion criteria were (1) serious health events (including but not limited to a myocardial infarction, cerebral apoplexy, a pulmonary embolism, and severe hepatic and renal dysfunction) < 3 months before admission, (2) a suspicion or diagnosis of malignancy at baseline, or (3) a life expectancy of no more than 6 months. In the current study, we also excluded patients who (1) already retired before onset of AICLI or reach retirement age (≥ 60 years old for men and ≥ 55 years old for women) by the 12-month follow-up, (2) lost to follow-up or died during the 12-month follow-up and (3) transferred to another hospital due to unrelieved ischemia or infection after discharge during the 12-month follow-up.

# 2.2. Procedures for Cell Transplantation

As previously described [4], subcutaneous injections of rhG-CSF (Neupogen®; Amgen, Thousand Oaks, CA, USA) (5–10 μg/kg per day for 4 days) was employed to mobilize the bone marrow cells and enoxaparin (4000IU/day) was employed to prevent hypercoagulable states. On the fifth day, a suspension of PBMNCs was collected via leukapheresis (COM.TEC; Fresenius Hemocare GmbH, Bad Homburg,

Germany). Then after washing 3 times and resuspending the apheresis products in an ethylenediaminetetra-acetic acid-phosphate buffered saline solution (200 mL) that contained 0.5% human albumin, the PBMNCs cell product was obtained. PCCs was obtained on the basis of PBMNCs by using a magnetic cell sorting system (Miltenyi-Biotec GmbH, BergischGladbach, Germany). The total cell count of $CD34^+$ cells was determined by leukocyte counting and flow cytometry. The cell products were transplanted into the ischemic limbs via equidistant intramuscular injections (0.5 mL/site) with patients under general anesthesia.

## 2.3. Data Collection

During hospitalization, patients' demographic characteristics, risk factors for cardio-cerebral-vascular diseases, diseases history, treatment history, educational background, etiology of AICLI, critical results of blood examination, etc. were recorded and patients were asked about their employment status and latest job before the onset of AICLI. The baseline features of the treated limb were also recorded, including numbers of involved limbs, the RC, the ankle-brachial index (ABI), the transcutaneous pressure of oxygen ($TcPO_2$) of the dorsum, and the occlusion level of the arteries according to the CTA, MRA and/or DSA.

## 2.4. Outcomes and Follow-up

The outcome was return to work (RTW), defined as part-time or full-time employment at 12 months after transplantation and classified as return to the same job, switch to an easier job (relevant with AICLI) and normal job change (irrelevant with AICLI). The time at which patients returned to work was also recorded. For patients did not return to work at 12 months after transplantation, reasons were classified as (1) unable to work owing to AICLI, (2) preferred not to work owing to AICLI (including full-time homemaker), (3) early retirement and (4) unable or not preferred to work owing to other reasons. Patients were required to pay regular clinical visit at 1, 3, 6, 12 months and then annually after transplantation. Data in terms of patients' employment status was asked and recorded during the clinical visit or via telephone.

## 2.5. Statistical Analysis

The quantitative data, which were compared using the Student t-test, are shown as mean ± standard deviation (SD) or as the median with the interquartile range (IQRs), depending on their distribution. Categorical variables, presented as frequencies and percentages, were compared using the $\chi^2$ test or Fisher exact test. Multivariable logistic regression was performed to identify the independent risk factors for RTW by stepwise selection of variables. Factors with a P value less than .10 in univariate analyses were introduced into the multivariate model. Cumulative incidence of RTW rate was analyzed by Kaplan–Meier analysis.All statistical tests were performed using a two-sided α of 0.05. All tests were performed using PASW software, version 19 (IBM Corporation, Armonk, NY, USA), or R, version 4.0.5.

# 3. Results

## 3.1. Baseline data

Between May 2009 to May 2021, 192 AICLI patients underwent cell transplantation in our center. After excluding those who were lost to the follow-up, retired before onset of AICLI reach retirement age during the 12-month follow-up, 171 patients with complete data at the 12-month follow-up were finally included and analyzed (Fig. 1). The mean age of the patients was 41.9 ± 9.6 years (range, 20–57 years), and the male ratio was 99.4% (170/171). The mean follow-up period was 57.9 ± 36.4 months (range 12–144 months). Among the 171 patients, 160 (93.6%) were married, 150 (87.7%) had children and 12 (7.0%) received college education. The patients were characterized with low frequencies of cardiovascular risk factors except for high frequencies of smoking history (141 patients [82.5%]). All patients were in critical limb ischemia (CLI) condition with RC 4 (22 patients [12.9%]) or 5 (149 patients [87.1%]) and most were TAO-induced (159 patients [93.0%]). There were 166 lower limbs and 13 upper limbs involved in the study. The median total $CD34^+$ cell count in the transplants was $40.4 \times 10^6$, with an IQR of $23.4–81.3 \times 10^6$. More details of the baseline characteristics were shown in Table 1.

Table 1
Comparison of Baseline Characteristics between 2 Groups of Patients

| | Total (n = 171) | RTW group (n = 119) | non-RTW group (n = 52) | P value |
|---|---|---|---|---|
| Demographic characteristics | | | | |
| Age, years, mean ± SD | 41.9 ± 9.6 | 40.9 ± 9.8 | 44.3 ± 8.9 | 0.033 |
| 20–29, n (%) | 23 (13.4) | 20 (16.8) | 3 (5.8) | 0.052 |
| 30–39, n (%) | 39 (22.8) | 29 (24.4) | 10 (19.2) | 0.461 |
| 40–49, n (%) | 68 (39.8) | 43 (36.1) | 25 (48.1) | 0.142 |
| 50–59, n (%) | 41 (24.0) | 27 (22.7) | 14 (26.9) | 0.551 |
| <40 years, n (%) | 62 (36.3) | 49 (41.2) | 13 (25.0) | 0.040 |
| ≥40 years, n (%) | 109 (63.7) | 70 (58.8) | 39 (75.0) | 0.043 |
| Gender, (male/female) | 170/1 | 118/0 | 51/1 | 0.131 |
| Body mass index, (kg/m$^2$) (mean ± SD) | 23.5 ± 3.2 | 23.5 ± 3.4 | 23.7 ± 2.7 | 0.636 |
| Married, n (%) | 160 (93.6) | 108 (90.8) | 51 (98.1) | 0.119 |
| Having children, n (%) | 150 (87.7) | 101 (84.9) | 49 (94.2) | 0.099 |
| College education, n (%) | 12 (7.0) | 10 (8.4) | 2 (3.8) | 0.283 |
| Occupation | | | | |
| Mental worker, n (%) | 41 (30.0) | 39 (32.8) | 2 (3.8) | 0.002 |
| Manual worker, n (%) | 82 (48.0) | 52 (43.7) | 30 (57.7) | 0.092 |
| Farmer, n (%) | 11 (6.4) | 6 (5.0) | 5 (9.6) | 0.262 |
| Self-employed, n (%) | 29 (17.0) | 18 (15.1) | 11 (21.2) | 0.334 |
| Other, n (%) | 8 (4.6) | 4 (3.4) | 4 (7.7) | 0.217 |

The data presented are the numbers (%) and the means ± standard deviations or medians and the interquartile ranges.

*: ABIs of 158 patients with lower limbs treated were included in this analysis, while the other 13 patients with upper limbs treated were excluded.

Abbreviations: RTW, return to work; non-RTW, not return to work; SD, standard deviation; AICLI, angiitis-induced critical limb ischemia; TAO, thromboangiitis obliterans; IQR, interquartile range; CRP, C-reactive protein; GHb, glycosylated hemoglobin; GFR, glomerular filtration rate; ESR, erythrocyte sedimentation rate.

| | Total (n = 171) | RTW group (n = 119) | non-RTW group (n = 52) | P value |
|---|---|---|---|---|
| Hometown region | | | | |
| Central, n (%) | 26 (15.2) | 18 (15.1) | 8 (15.4) | 0.965 |
| East, n (%) | 124 (72.5) | 89 (74.8) | 35 (67.3) | 0.313 |
| West, n (%) | 21 (12.3) | 12 (10.1) | 9 (17.3) | 0.186 |
| Cardiovascular risk factors | | | | |
| Smoking history, n (%) | 141 (82.5) | 99 (83.2) | 42 (80.8) | 0.701 |
| Hypertension, n (%) | 12 (7.0) | 8 (6.7) | 4 (7.7) | 0.819 |
| Diabetes mellitus, n (%) | 12 (7.0) | 9 (7.6) | 3 (5.8) | 0.673 |
| Hyperlipidaemia, n (%) | 15 (8.8) | 10 (8.4) | 5 (9.6) | 0.797 |
| Cause of AICLI | | | | |
| TAO, n (%) | 159 (93.0) | 112 (94.1) | 47 (90.4) | 0.379 |
| Other, n (%) | 12 (7.0) | 7 (5.9) | 5 (9.6) | 0.379 |
| Medication history | | | | |
| Antiplatelet drugs, n (%) | 104 (60.8) | 77 (70.6) | 27 (51.9) | 0.115 |
| Vasodilator, n (%) | 39 (22.8) | 19 (16.0) | 13 (25.0) | 0.164 |
| Warfarin/Rivaroxaban, n (%) | 18 (10.5) | 11 (9.2) | 7 (13.5) | 0.408 |
| Surgical history | | | | |
| Bypass, n (%) | 6 (3.5) | 4 (3.4) | 2 (3.8) | 0.874 |
| Endarterectomy, n (%) | 1 (0.6) | 0 (0.0) | 1 (1.9) | 0.129 |
| Stent grafting, n (%) | 8 (4.7) | 4 (3.4) | 4 (7.7) | 0.217 |
| Balloon angioplasty, n (%) | 25 (14.6) | 18 (10.5) | 7 (13.5) | 0.777 |

The data presented are the numbers (%) and the means ± standard deviations or medians and the interquartile ranges.

*: ABIs of 158 patients with lower limbs treated were included in this analysis, while the other 13 patients with upper limbs treated were excluded.

Abbreviations: RTW, return to work; non-RTW, not return to work; SD, standard deviation; AICLI, angiitis-induced critical limb ischemia; TAO, thromboangiitis obliterans; IQR, interquartile range; CRP, C-reactive protein; GHb, glycosylated hemoglobin; GFR, glomerular filtration rate; ESR, erythrocyte sedimentation rate.

| | Total (n = 171) | RTW group (n = 119) | non-RTW group (n = 52) | P value |
|---|---|---|---|---|
| Thrombolysis, n (%) | 26 (15.2) | 17 (9.9) | 9 (17.3) | 0.613 |
| Thrombectomy, n (%) | 12 (7.0) | 8 (4.7) | 4 (7.7) | 0.819 |
| Toe amputation, n (%) | 19 (11.1) | 13 (10.9) | 6 (11.5) | 0.906 |
| Blood examination, n (%) | | | | |
| Fibrinogen, mg/dL, (median, IQR) | 321.5 (257–408) | 307 (244–388) | 354 (292–477) | < 0.001 |
| CRP, mg/L, (median, IQR) | 5.4 (1.8–14.8) | 4.5 (1.55–11.65) | 8.2 (2.3–18.7) | 0.022 |
| Glucose, mmol/L, (median, IQR) | 4.7 (4.4–5.2) | 4.7 (4.4–5.1) | 4.8 (4.6–5.3) | 0.915 |
| GHb, %, (median, IQR) | 5.4 (5.2–5.7) | 5.45 (5.2–5.7) | 5.4 (5.25–5.60) | 0.359 |
| Creatinine, μmol/L, (median, IQR) | 71.5 (64–82) | 72 (65–82) | 71 (63–82) | 0.600 |
| GFR, mL/min, (median, IQR) | 107 (99–119) | 107 (97–117) | 109 (101.5–120) | 0.222 |
| ESR, mm/h, (median, IQR) | 14 (7–30) | 14.5 (7–32) | 13 (6–26) | 0.453 |

The data presented are the numbers (%) and the means ± standard deviations or medians and the interquartile ranges.

*: ABIs of 158 patients with lower limbs treated were included in this analysis, while the other 13 patients with upper limbs treated were excluded.

Abbreviations: RTW, return to work; non-RTW, not return to work; SD, standard deviation; AICLI, angiitis-induced critical limb ischemia; TAO, thromboangiitis obliterans; IQR, interquartile range; CRP, C-reactive protein; GHb, glycosylated hemoglobin; GFR, glomerular filtration rate; ESR, erythrocyte sedimentation rate.

# 3.2. RTW

All patients lost the ability to work before admission. A total of 119 patients who returned to work within 12 months after cell transplantation were included in RTW group and the remaining 52 in not return to work (non-RTW) group. The 12-month and 24-month RTW cumulative rates were 69.4% (95% confidence interval [CI] 61.6%-75.6%) and 70.1% (95% CI 62.3%-76.2%), respectively (Fig. 2). Among the 119 RTW patients, 82 patients (68.9%) return to their preoperative jobs, 25 patients (21.0%) switch to easier jobs which require fewer physical demands and 12 patients (10.1%) change their jobs for AICLI-unrelated reasons (Table 3). Fifty-two patients failed to return to work within 12 months after cell transplantation, among whom 19 patients (36.6%) were unable to work, 6 patients (11.5%) retired early, and 19 patients

(36.5%) preferred not to work owing to AICLI. The remaining 8 patients (15.4%) were unable or preferred not to work owing to other reasons (1 for femoral fracture, 2 for anterior circulation cerebral infarction, 2 for COVID-19 epidemic, 1 for injury of common peroneal nerve and 2 for family affairs) (Table 3).

Table 2
Comparison of Characteristics of Ischemic Limbs and Autoimplants between 2 Groups of Patients

| | Total (n = 171) | RTW group (n = 119) | non-RTW group (n = 52) | P value |
|---|---|---|---|---|
| Number of ischemic limbs | | | | |
| 1 | 136 (79.5) | 93 (78.1) | 43 (82.7) | 0.498 |
| 2 | 30 (17.5) | 22 (18.5) | 8 (15.4) | 0.625 |
| 3 | 3 (1.8) | 2 (1.7) | 1 (1.9) | 0.912 |
| 4 | 2 (1.2) | 2 (1.7) | 0 (0.0) | 0.347 |
| Ulcer without gangrene, n (%) | 67 (39.2) | 49 (41.2) | 18 (34.6) | 0.419 |
| Gangrene, n (%) | 82 (48.0) | 53 (44.5) | 29 (55.8) | 0.176 |
| Upper limbs involved, n (%) | 13 (7.6) | 10 (9.7) | 3 (5.8) | 0.550 |
| Lower limbs involved, n (%) | 166 (97.1) | 115 (96.6) | 51 (98.1) | 0.608 |
| Highest level of arterial occlusion | | | | |
| Iliac artery, n (%) | 6 (3.5) | 4 (3.3) | 2 (3.8) | 0.874 |
| Femoral/brachial artery, n (%) | 70 (40.9) | 43 (36.1) | 27 (51.9) | 0.053 |
| Popliteal artery, n (%) | 26 (15.2) | 22 (18.4) | 4 (7.7) | 0.065 |
| Below the knee or elbow, n (%) | 69 (40.4) | 50 (42.0) | 19 (36.5) | 0.502 |
| Iliac/femoral/brachial artery, n (%) | 76 (44.4) | 47 (39.5) | 29 (55.8) | 0.050 |
| Popliteal/below the knee or elbow artery, n (%) | 95 (55.6) | 72 (60.5) | 23 (44.2) | 0.050 |
| Rutherford class | | | | |
| 4, n (%) | 22 (12.9) | 17 (14.3) | 5 (9.6) | 0.401 |
| 5, n (%) | 149 (87.1) | 102 (85.7) | 47 (90.4) | 0.401 |

The data presented are the numbers (%) and the means ± standard deviations or medians and the interquartile ranges.

*: ABIs of 158 patients with lower limbs treated were included in this analysis, while the other 13 patients with upper limbs treated were excluded.

Abbreviations: RTW, return to work; non-RTW, not return to work; IQR, interquartile range; ABI, ankle-brachial index; $TcPO_2$, transcutaneous oxygen pressure; PBMNCs, peripheral blood mononuclear cells; PCCs, purified $CD34^+$ cells.

| | Total (n = 171) | RTW group (n = 119) | non-RTW group (n = 52) | P value |
|---|---|---|---|---|
| Ulcer/gangrene | | | | |
| Ulcer/gangrene with infection | 23 (13.4) | 10 (8.4) | 13 (25.0) | 0.011 |
| Ulcer/gangrene without infection | 126 (73.7) | 92 (77.3) | 34 (65.4) | 0.103 |
| Without ulcer/gangrene | 22 (12.9) | 17 (14.3) | 5 (9.6) | 0.401 |
| ABI*, (median, IQR) | 0.49 (0.37–0.64) | 0.48 (0.37–0.61) | 0.53(0.35–0.81) | 0.062 |
| $TcPO_2$, mmHg, (median, IQR) | 19 (10–28) | 18.5 (10–28) | 19 (5–30) | 0.496 |
| Cell product | | | | |
| Type | | | | |
| PBMNCs, n (%) | 97 (56.7) | 69 (58.0) | 28 (53.8) | 0.615 |
| PCCs, n (%) | 74 (43.3) | 50 (42.0) | 24 (46.2) | |
| $CD34^+$ cells, ($10^6$), (median, IQR) | 40.4 (23.4–79.1) | 43.8 (25.4–97.2) | 29.8 (15.3–52.9) | 0.002 |
| $CD34^+$ cells/kg, ($10^5$/Kg), (median, IQR) | 5.8 (3.2–11.0) | 6.8 (3.6–12.0) | 4.6 (2.5–8.2) | 0.012 |
| Cell viability, %, (median, IQR) | 98.4 (97.4–98.8) | 98.4 (97.1–98.9) | 98.2 (97.7–98.6) | 0.826 |

The data presented are the numbers (%) and the means ± standard deviations or medians and the interquartile ranges.

*: ABIs of 158 patients with lower limbs treated were included in this analysis, while the other 13 patients with upper limbs treated were excluded.

Abbreviations: RTW, return to work; non-RTW, not return to work; IQR, interquartile range; ABI, ankle-brachial index; $TcPO_2$, transcutaneous oxygen pressure; PBMNCs, peripheral blood mononuclear cells; PCCs, purified $CD34^+$ cells.

Table 3
Working Status for AICLI Patients at 12 Months after Cell Transplantation

| Working status | n = 171 |
|---|---|
| RTW | |
| Return to the same work, n (%) | 82 (48.0) |
| Change work owing to AICLI, n (%) | 25 (14.6) |
| Change work owing to other reasons, n (%) | 12 (7.0) |
| Non-RTW | |
| Unable to work owing to AICLI, n (%) | 19 (11.1) |
| Early retirement, n (%) | 6 (3.5) |
| Prefer not to work owing to AICLI, n (%) | 19 (11.1) |
| Unable or preferred not to work owing to other reasons, n (%) | 8 (4.7) |

Abbreviations: AICLI, angiitis-induced critical limb ischemia; RTW, return to work; non-RTW, not return to work.

# 3.3. Characteristics of RTW group and non-RTW group

The mean age of the RTW group tended to be lower than that of the non-RTW group (40.9 ± 9.8 versus 44.3 ± 8.9 years, P = 0.033) and the frequency of the patients whose ages were < 40 years in the RTW group was significantly higher than that in the non-responder group (41.2% versus 25.0%, P = 0.040) (Table 1). In addition, significant difference was also observed in terms of the type of perioperative occupation between the 2 groups (Table 1). Though manual worker took the largest proportion in both groups, the proportion of mental worker was significantly lager in RTW group (32.8% versus 3.8%, P = 0.002). When the blood examinations were evaluated, patients in RTW group had significantly lower CRP and blood fibrinogen levels than non-RTW group (P = 0.022 and P < 0.001, respectively) (Table 1). No significant differences were observed between RTW group and non-RTW group in terms of other sociodemographic characteristics, the etiologies, risk factors of cardiovascular disease, treatment histories (Table 1).

Regarding the ischemic limbs, no significant differences were observed in terms of the number of ischemic limbs, the RC, upper/lower limbs involved and test results such as ABI and $TcPO_2$. Considering the highest level of arterial occlusion, 5 (2.9%) patients were with occlusion in iliac artery (include common and external iliac arteries), 71 (41.5%) in femoral (included common femoral artery and superficial femoral artery)/brachial artery, 26 (15.2%) in popliteal artery and 69 (40.4%) in arteries below the knee or elbow. Though with no significant difference observed between the 2 groups in terms of the highest level of arterial occlusion, RTW group was characterized by a significantly higher percentage of patients in whom the highest arterial occlusion level was at popliteal/below the knee or elbow arteries

(60.5% versus 44.2%, P = 0.050) (Table 2). Though no significant difference was observed in terms of RC between the 2 groups (P = 0.401), among 150 patients with ulcer or gangrene (RC 5), 23 patients (13.4%) were also complicated with perioperative infection and a significantly lower percentage of patients with perioperative ulcer/gangrene infection was observed in RTW group (8.4% versus 25.0%, P = 0.011) (Table 2). In terms of cell product, RTW patients were observed with a significantly higher dosage of the total amount of CD34 + cells transplanted ($43.8\times10^6$ [$25.4–97.2\times10^6$] versus $29.8\times10^6$ [$15.3–52.9\times10^6$], P = 0.002) and amount of CD34 + cells transplanted per Kg ($6.8\times10^5$/Kg [$3.6–12.0\times10^5$/Kg] versus $4.6\times10^5$/Kg [$2.5–8.2\times10^5$/Kg], P = 0.012).

# 3.4. Multivariate analysis

According to the results of the univariate logistic regression, several variables were screened out: age ≥ 40 years (odds ratio [OR] 2.107, 95% CI 1.034–4.293, P = 0.040), married (OR 0.193, 95% CI 0.024–1.532, P = 0.119), having children (OR 0.344, 95% CI 0.097–1.222, P = 0.099), highest arterial occlusion level at popliteal/below the knee or elbow arteries (OR 1.932, 95% CI 0.990–3.734, P = 0.050), perioperative limb infection of patients with ulcer or gangrene (OR 0.306, 95% CI 0.123–0.763, P = 0.011), preoperative occupation as mental workers (OR 7.962, 95% CI 2.334–27.159, P = 0.002), fibrinogen > 4g/L (OR 0.453, 95% CI 0.218–0.939, P = 0.033), CRP > 3mg/L (OR 0.589, 95% CI 0.284–1.223, P = 0.156), and base-10 logarithm (Log) of total amount of transplanted CD34 + cells (OR 2.824, 95% CI 1.337–5.961, P = 0.006) and Log of total amount of transplanted CD34 + cells per Kg (OR 2.439, 95% CI 1.167–5.099, P = 0.018) (Table 4). After multivariate logistic analysis, age ≥ 40 years (OR 2.659, 95% CI 1.138–6.719, P = 0.029), perioperative limb infection of patients with ulcer or gangrene (OR 0.250, 95% CI 0.075–0.779, P = 0.019) and preoperative job as mental workers (OR 8.930, 95% CI 2.665–42.847, P = 0.002) were identified as independent risk factors for RTW (Table 4).

Table 4
Univariate and Multivariate Logistic Regression Analysis of Independent Risk Factors

| Candidate Variable | Univariate Analysis | | Multivariate Analysis | |
|---|---|---|---|---|
| | OR (95% CI) | P value | OR (95% CI) | P value |
| Age ≥ 40 years | 2.107 (1.034–4.293) | 0.040 | 2.659 (1.138–6.719) | 0.029 |
| Married | 0.193 (0.024–1.532) | 0.119 | | |
| Having children | 0.344 (0.097–1.222) | 0.099 | | |
| Preoperative occupation as mental workers | 7.962 (2.334–27.159) | 0.002 | 8.930 (2.665–42.847) | 0.002 |
| CRP > 3mg/L | 0.589 (0.284–1.223) | 0.156 | | |
| Fibrinogen > 4g/L | 0.453 (0.218–0.939) | 0.033 | | |
| Highest arterial occlusion level at popliteal/below the knee artery | 1.932 (0.999–3.734) | 0.050 | | |
| Ulcer/gangrene with infection | 0.306 (0.123–0.763) | 0.011 | 0.250 (0.075–0.779) | 0.019 |
| Log (total transplanted CD34 + cell counts per Kg)* | 2.439 (1.167–5.099) | 0.018 | | |
| Log (total transplanted CD34 + cell counts)** | 2.824(1.337–5.961) | 0.006 | | |
| * Base-10 logarithm of total transplanted $CD34^+$ cell counts per Kg. | | | | |
| ** Base-10 logarithm of total transplanted $CD34^+$ cell counts. | | | | |
| Abbreviations: OR, odds ratio; CI, confidential interval; CRP, C-reaction protein. | | | | |

# 4. Discussion

Due to poor anatomical conditions and a high postoperative re-occlusion rate, 20–50% of CLI patients, which are also called no-option CLI (NO-CLI) patients, are not suitable for traditional interventions such as surgical or endovascular treatment.[13] AICLI, which shows a propensity for affecting the distal small or microvessels and destroying the anatomic run-off, composes a remarkable proportion of the NO-CLI population. However, AICLI patients, in which most patients were TAO-induced, were characterized with young age and a large proportion of males. In the current study, 171 patients (170 were male) with a mean age of 41.9 ± 9.6 years were enrolled and analyzed. Therefore, successful RTW is of vital

significance not only to AICLI patients and their families but also to the society. In this single center retrospective study, approximately two thirds of the patients returned to work in the year after hospitalization for AICLI, indicating that cell therapy could not only achieve the recovery of physical well-being but also satisfactory psychological health.

Vohra et al. reported that the postoperative employment status of patients with claudication who underwent lower limb revascularization was positively influenced by younger age.[14] Burger et al. reported that patients' RTW after limb amputation depended on general factors including age.[15] In the current study, age ≥ 40 years old was a negative independent risk factor for AICLI patients' RTW within 12 months. We infer the role that age played in the RTW progress might be explained with several aspects. First, the relief of ischemia was partly up to the function of cell product including angiogenesis and vasculogenesis. The auto-implants of aged patients were reported to be related to impaired angiogenic potency and younger age was reported to be associated with better therapeutic effect of cell therapy in the treatment of NO-CLI patients.[16–20] Second, younger patients were characterized with better general condition and less comorbidities, thus lowering the risk of adverse events including death, organ dysfunction and cardio-cerebrovascular diseases which might occur during the follow-up and further stop patients from RTW. In 2019, we reported a study in terms of factors associated with the 6-month CLI remission among AICLI patients who underwent cell transplantation.[21] In the previous study, age ≥ 50 years old was reported to be the independent factors of the 6-month CLI remission. However, in the current study, the age identified was younger (40 years old). We speculate that this may be partly explained by the fact that AICLI patients in their 50s are more likely to retire early even after total relief of CLI, given that the legal retirement age in China is 60 years old (for men).[22] Though in studies in terms of RTW of patients with coronary heart diseases or cerebral artery diseases, age was seldom reported to be a predictive factor ,[23–27] considering that cardio-cerebrovascular diseases tended to occur in the elderly and most patients they enrolled in the studies were over 50 years old, it's reasonable that younger age was not reported to be associated with RTW.

Patients' preoperative job type, together with education and income, are important indicators of socioeconomic status, and it may capture some or all of the effect of income and education.[28] Some studies also reported that different job types to be indicators of patients' RTW after orthopedic surgery.[29,30] In the current study, preoperatively working as a mental worker was identified as a positive independent risk factor for patients' RTW. This can be reasonable, for that mental work generally demand less physical expenditure compared with other types of work thus lowering the physical threshold needed for RTW. Among all the job types in the current study, mental worker was the one with not only the highest RTW ratio (39/41, 95.1%) but also the highest return to the same work ratio (31/41, 75.6%). In contrast, for jobs which require a certain amount of physical activity, including manual worker and farmer, the proportion of non-RTW patients and patients who change work owing to AICLI were relatively high. Like we mentioned before, job type could also reflect worker's education to some extent. Jiang et al. reported that college education was associated with a higher likelihood of return to work after acute myocardial infarction.[23] Wang et al. reported higher educational level was a significant factor associated with RTW in

patients with severe traumatic brain injury.[31] In the current study, 7.0% (12/171) of patients were with a bachelor degree and RTW was achieved in 10 patients in whom 8 were preoperatively working as metal workers.

Out of 171 patients, 150 (87.7%) were in RC 5 with an ulcer/gangrene at admission and 13.4% (23/171) of them were with infection during the perioperative period. Infection is a factor which generally increases oxygen consumption further aggravates the ischemic degree and tissue loss in patients with CLI. Lu et al. reported that infection was an important independent risk factors of amputation in patients with diabetes-induced CLI.[32] On the other hand, patients with limb infection often require relative long-term anti-infective treatment including antibiotics treatment, regularly dressing change and even elective debridement. This process not only prolongs the time period for rehabilitation but also makes patients pay over attention to their ischemic limbs for fear of recurrence thus delaying or even canceling their plans to RTW.

RTW is associated with the relief of ischemia after cell transplantation. However, not all patients return to work after total relief of CLI. Many RTW patients claimed to be free of pain in the transplanted limb and started working again within the 12-month follow-up while a 2-class pians evaluated by Wong-Baker FACES Pain Rating Scale (WBFPS) could still be observed. On the other hand, there were also many patients who were resistant to re-employment even after total relief of limb ischemia and one was even diagnosed with depression. Therefore, both physical and mental well-being are essential for RTW and considering the fact that the retirement age for many jobs in China has been increasing to 65 years, RTW will be a more and more important indicator in measuring treatment methods.

The biggest limitation of the current study lies in its essence as a single-center retrospective study. However, as to our knowledge, there is little studies focusing on the postoperative RTW for CLI patients, especially AICLI patients, who underwent cell transplantation.

# 5. Conclusion

AICLI patients who underwent cell transplantation were with a satisfactory mid-term RTW cumulative rate. AICLI patients < 40 years old with preoperative occupation as mental worker were more likely to return to work within 12 months after cell transplantation. For AICLI patients, prevention of limb infection during the perioperative period is of great significance to RTW.

# List Of Abbreviations

RTW
return to work;
AICLI
angiitis-induced critical limb ischemia;
PCCs

purified CD34 + cells;
PBMNCs
peripheral blood mononuclear cells.

# Declarations

### Ethics approval and consent to participate

The study design was approved by the Ethics Committee of Zhongshan Hospital, Fudan University, Shanghai, China. All included patients were informed about the nature of the study and gave their written informed consent.

### Consent for publication

All patients signed a consent form for their data to be used for research or publication.

### Availability of data and materials

Due to the confidential and identifiable nature of this dataset, data sharing will not be available. All authors have accessed the database and verified its accuracy.

### Competing interests

All authors declare no competing interests.

### Funding

This work was supported by China National Natural Science Funds (Grant No. 81970407; 81900426), Grants from Shanghai Excellent Academic Leader (No. 19XD1401200) and Fudan University “Star of Tomorrow” Famous Doctor Training Project (2019).

### Authors' contributions

H L: Conception and design, collection and assembly of data, data analysis and interpretation and manuscript writing.

Y L: Conception and design, collection and assembly of data, data analysis and interpretation and manuscript writing.

T P: Conception and design, collection and assembly of data, data analysis and interpretation and manuscript writing.

Y F: Collection and assembly of data, data analysis and interpretation.

G F: Collection and assembly of data, data analysis and interpretation.

X J: Collection and assembly of data, data analysis and interpretation.

B C: Administrative support and manuscript writing.

Z W: Collection and assembly of data, data analysis and interpretation.

S G: Collection and assembly of data, data analysis and interpretation.

P L: Administrative support and conception and design.

W F: Administrative support, final approval of manuscript and data analysis and interpretation.

Z D: Conception and design, administrative support, final approval of manuscript, manuscript writing and financial support.

**Acknowledgement**

Not applicable

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# Figures

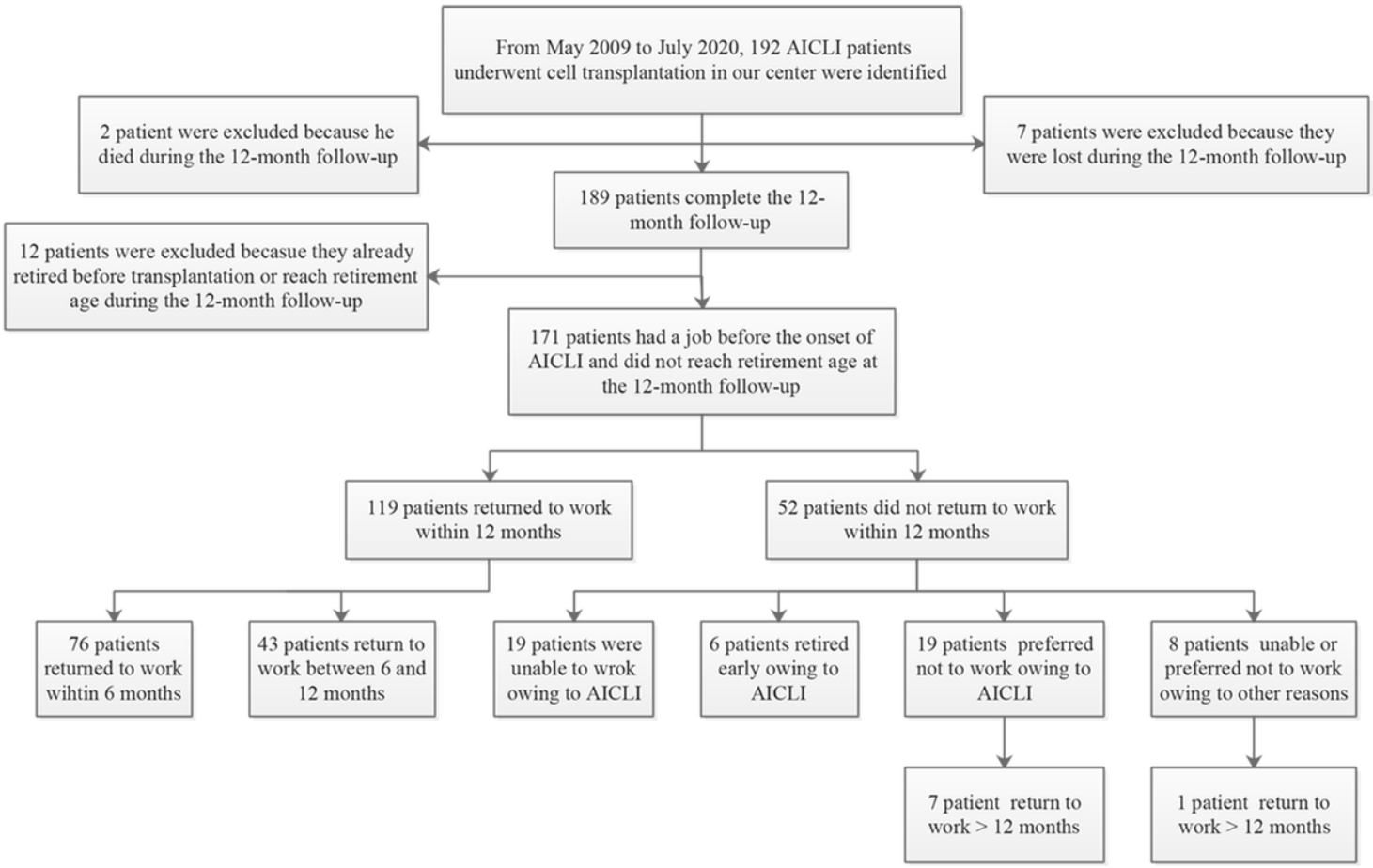


**Figure 1**

Protocol of current study. AAbreviations: AICLI, angiitis-induced critical limb ischemia.

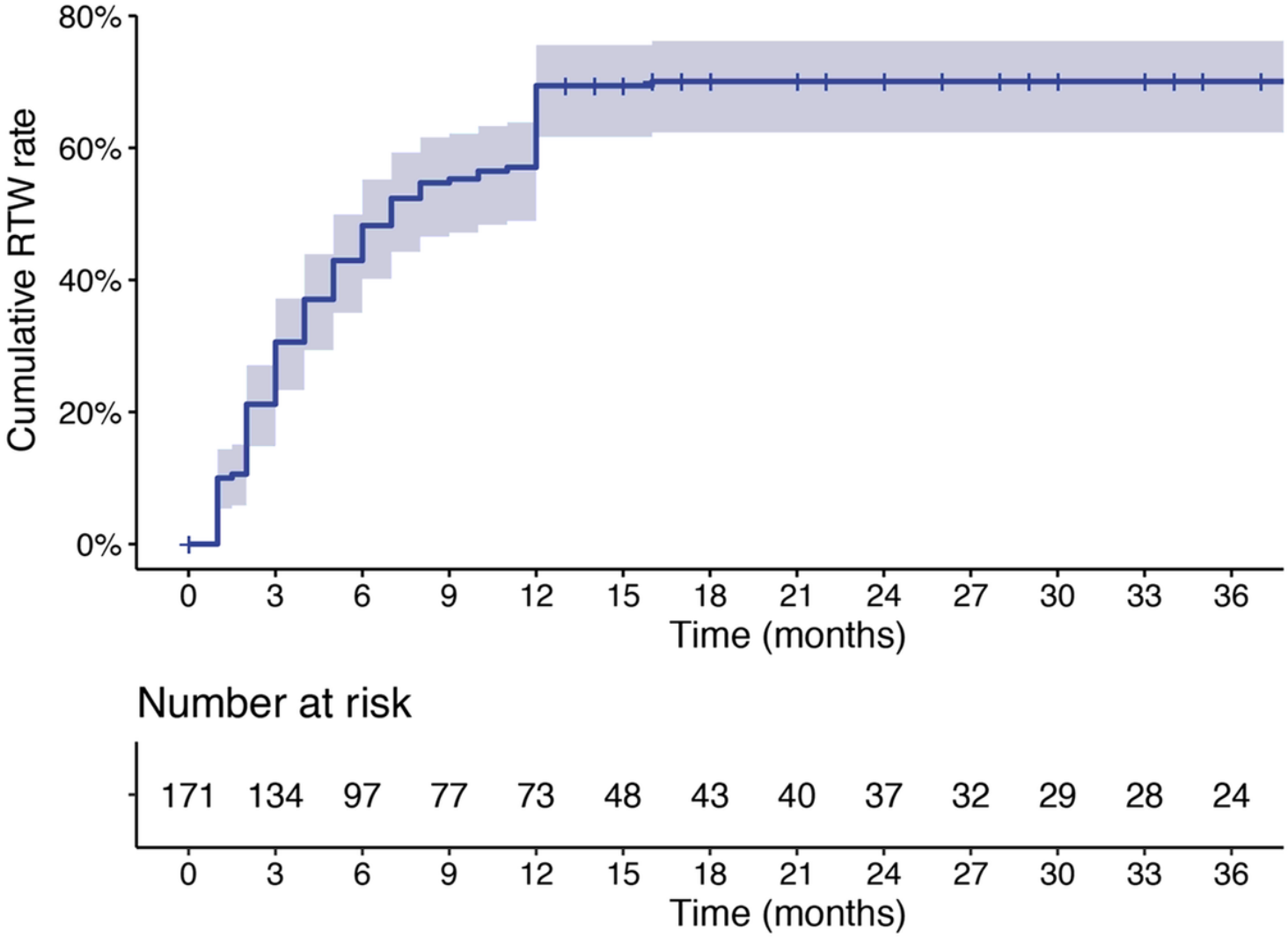


**Figure 2**

Kaplan-Meier curves showing the probabilities of cumulative RTW rate. Abbreviations: RTW, return to work.