Risk and Prognostic Factors of Replantation Failure in Patients With Severe Traumatic Major Limb Mutilation: a Retrospective Cohort Study

Chang Gao
Suzhou Dushu Lake Hospital
Ling Yang
Soochow University Medical College
Jihui Ju
First Affiliated Hospital of Soochow University
Keran Zhang
First Affiliated Hospital of Soochow University
Mingming Wu
ruihua affiliated hospital of soochow university
Lijuan Yang
Soochow University Medical College
Xiaoting Lu
Suzhou dushu lake hospital
Ruixing Hou
Ruihua affiliated hospital of soochow university
Qiang Guo (guojiang@suda.edu.cn)
First Affiliated Hospital of Soochow University https://orcid.org/0000-0002-2326-2244

Research

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Abstract

Background: Traumatic mutilation of major limbs can result in limb loss, motor disability, or even death. Despite advancements in treatment, replantation failure could result in additional financial burden and severe psychosocial pressure on patients. Here, we determine the risk and prognostic factors of replantation failure in patients with traumatic major limb mutilation.

Methods: In this retrospective cohort study, severed adult inpatients with traumatic major limb mutilation who underwent replantation from three hospitals in the Suzhou Ruixing Medical Group were included. Data obtained from electronic medical records were used to analyze predictors and risk factors for replantation failure.

Results: From the 66 patients included, replantation failure occurred in 48 patients (72.7%). The area under the curve of the joint prediction of lactic acid on admission, 72 h cumulative fluid balance, and albumin level immediately postoperatively was 0.838 (95% CI, 0.722-0.954; $P < 0.001$) with a sensitivity of 89.7% and a specificity of 69.2%. Lower limb trauma (OR 8.65, 95%CI 1.64-45.56, $P = 0.011$), mangled extremity severity scores (OR 2.24, 95%CI 1.25-4.01, $P = 0.007$), and first 72 h cumulative fluid balance > 4885.6 ml (OR 10.25, 95%CI 1.37-76.93, $P = 0.024$) were independent risk factors for replantation failure.

Conclusions: Lower limb trauma, mangled extremity severity scores, and cumulative water balance were associated with replantation failure. This implies that fluid management is necessary for major limb salvage. More studies are needed to explore the predictive power of indicators related to tissue oxygenation and wound healing for replantation failure.

Background

Traumatic mutilation of the major limbs is a life - and limb-threatening injury that may result in death, limb loss, or persistent functional motor disability [1–3]. Management involves bone fixation, interventional or surgical revascularization, and complex wound care that treats infections and segmental loss of bones, muscles, and nerves [1]. For patients with persistent infection, open wounds, and replantation failure, additional treatment via debridement, flap covering, and/or amputation is required. These problems can impose severe physical, psychological, financial, and social distress on the patients [4–6].

Previous studies have shown that age, high injury severity score, blunt trauma, injury location, duration of ischemia, and reperfusion injury are associated with replantation failure and delayed amputation [4, 7, 8]. With the development of treatment for vascular, bone, nerve, and soft tissue injuries, injury severity scores such as mangled extremity severity scores (MESS) have varied in predicting the prognosis of amputation and replantation [4, 9–12]. Management of severely injured limbs remains a major challenge [13]. Here, we identify the risk and prognostic factors of replantation failure in patients who had traumatic mutilation of major limbs.

Methods

This was a multicenter retrospective cohort study. This study included all adult patients (age ≥ 18 years old) who had traumatic mutilation of major limbs (defined as an amputation between the trunk and the wrist or ankle) and underwent replantation [14, 15] between October 18, 2016, and July 31, 2020 from three hospitals in the Suzhou Ruixing Medical Group (Ruihua Affiliated Hospital of Soochow University, Ruixing Hospital, and Suzhou Ruihua Yingchun Hospital). All enrolled patients were admitted to the intensive care unit (ICU) because of their critical conditions. The medical group includes Level III specialized hospitals, rehabilitation hospitals, and an institute of applied technology in hand surgery. The focus medical programs of the group are orthopedic trauma, amputated limbs (fingers and toes) replantation, and rehabilitation, with an average annual operation volume of more than 10,000. All the mutilation limbs were accompanied by discontinuous vessels, nerves, muscles, and bone structures to varying degrees. Patients with severe limb damage that could not be replanted or had first-stage amputations were excluded. Patients who underwent replantation were identified by reviewing and analyzing admission logs and histories from all available electronic medical records and patient care resources.

Medical records were reviewed by trained physicians. Demographic and clinical characteristics of the patients were collected. Clinical characteristics included traumatic conditions, first (immediate postoperative) laboratory findings, MESS, 72-hour cumulative fluid balance after admission, treatments, and outcomes. Patients were followed up from admission to hospital discharge. The primary outcome was the replantation failure rate during hospitalization. Replantation failure was identified in patients with signs of any partial/total necrosis or capillary refill loss [16]. Delayed amputations were defined as amputations performed within the same hospitalization period after replantation [17]. All patients with replantation failure required additional surgery at least once. The secondary outcomes were the length of ICU stay and hospital stay.

Frequency data were expressed as proportions. Continuous data are presented as median (interquartile range [IQR]) if they were shown as a skewed distribution. Differences in categorical variables were assessed using the χ^2 test, while comparisons of continuous variables were made using the Mann-Whitney U test, as appropriate. Receiver operating characteristic (ROC) curves were used to explore the predictors and their cut-off values for replantation failure. The area under the curve (AUC) of ROC was used to evaluate predictive power. Multivariate logistic regression models were constructed to obtain the prediction probability while the AUCs of the ROC were used to evaluate the effectiveness of the combined predictions.

Multivariate logistic regression models were used to determine the independent risk factors for necrosis after replantation. Variables with $P < 0.2$ in univariate logistic regression were included in the multivariate analysis. The probabilities of entering and removing variables in a stepwise manner in the multivariate model were 0.05 and 0.10, respectively.

Data were analyzed using SPSS (version 25.0; IBM, Chicago, IL, USA). Statistical charts were generated using StataMP 16 (StataCorp, College Station, Texas, USA) and GraphPad Prism 7 (GraphPad Software, San Diego, CA, USA). A two-tailed *P* value of < 0.05, was considered statistically significant.

This study was approved by the Institutional Review Boards of the Suzhou Ruixing Medical Group (2021023).

Results

Clinical characteristics

During the four-year study period, 88 patients were admitted to the hospital after experiencing traumatic major limb mutilation. A total of 22 patients who had either severe limb damage that could not be replanted or first-stage amputations were excluded. The remaining 66 patients who underwent replantation were included in this study (Fig. 1).

The median age was 47.0 years old and most of which were males (n = 48, 72.7%). The distribution of patients in terms of injury was as follows: 32 (48.5%) had lower limb trauma, 64 (97.0%) had blunt trauma, and 29 (43.9%) had total mutilation. Most patients experienced blunt trauma with moderate-to-severe contamination. The median MESS was 10.0 points (IQR, 9.0-11.3 points) (Tables 1 and 2). Replantation failed in 48 (72.7%) patients, of whom 41 (62.1%) had partial necrosis and 7 (delayed amputation rate, 10.6%) had whole limb necrosis. In the cases of replantation failure, 11 cases were complicated by bacterial infection at the surgical site, 7 had thrombosis, and 1 had vascular crisis. All patients who failed replantation underwent one or more surgeries after replantation, including amputation, debridement, flap transplantation, and vacuum sealing drainage (VSD).

Table 1
The severed part of 66 patients with replantation of severed limb.

Severed part of limb	Number of patients
Forearm	21
Elbow	3
Upper arm	6
Shoulder	1
Forearm + upper arm	1
Wrist + forearm	2
Ankle	22
Shank	7
Thigh	3

Table 2
Clinical characteristics of 66 patients with replantation of severed limb.

Characteristics	All patients (n = 66)	Failure (n = 48)	Success (n = 18)	*P*
Age, median (IQR), yr	47.0 (36.0-54.5)	48.0 (38.0–56.0)	40.0 (28.5–52.5)	0.277
Sex, male patients, n (%)	48 (72.7)	38 (79.2)	10 (55.6)	0.108 [b]
Traumatic condition				
Lower limb, n (%)	32 (48.5)	27 (56.3)	5 (27.8)	0.039
Blunt mutilation, n (%)	64 (97.0)	48 (72.7)	16 (24.2)	0.071 [c]
Total mutilation, n (%)	29 (43.9)	22 (45.8)	7 (38.9)	0.613
Platelet count, × 10^9/L, median (IQR) [a]	123.5 (68.5-195.3)	103.0 (60.0-178.0)	162.5 (101.3-245.3)	0.014
RBC count, × 10^{12}/L, median (IQR) [a]	3.0 (2.5–3.8)	2.8 (2.3–3.4)	3.3 (3.0-4.1)	0.022
Albumin, g/L, median (IQR) [a]	27.0 (23.3–33.4)	25.8 (21.9–32.6)	32.7 (29.3–35.7)	0.002
Lactic acid on admission, mmol/L, median (IQR)	2.7 (1.2–4.6)	3.5 (1.4–4.8)	1.4 (0.9-3.0)	0.017
MESS, median (IQR)	10.0 (9.0-11.3)	11.0 (10.0–12.0)	9.0 (7.0–10.0)	< 0.001
Treatment and outcomes, median (IQR)				
Red cells suspension injected during surgery, ml	800.0 (375.0-1600.0)	850.0 (600.0-1750.0)	400.0 (0.0-900.0)	0.028

[a] First laboratory findings after surgery.

[b] Yates's correction was used.

[c] Fisher's exact test was used.

Abbreviations: IQR, interquartile range; RBC, red blood cell; MESS, mangled extremity severity score.

Characteristics	All patients (n = 66)	Failure (n = 48)	Success (n = 18)	*P*
Hetastarch injected during surgery, ml	1000.0 (500.0-1500.0)	1000.0 (1000.0-1500.0)	1000.0 (500.0-1000.0)	0.015
72 hours cumulative fluid balance after admission, ml	5101.5 (2761.2-7953.8)	5727.5 (3148.0-8589.0)	3041.0 (351.0-4663.2)	0.006
Length of hospital stay, day	51.5 (26.8–69.0)	57.0 (43.3–77.5)	25.0 (18.8–39.5)	< 0.001
[a] First laboratory findings after surgery.				
[b] Yates's correction was used.				
[c] Fisher's exact test was used.				
Abbreviations: IQR, interquartile range; RBC, red blood cell; MESS, mangled extremity severity score.				

Patients with replantation failure had a higher proportion of lower limb trauma (56.3% vs. 27.8%, $P = 0.039$) than those in the successful group (Table 2). Failure group presented higher median values of lactic acid on admission (3.5 vs. 1.4 mmol/l, $P = 0.017$), MESS (11.0 vs. 9.0, $P < 0.001$), red cells suspension injected during surgery (850.0 vs. 400.0 ml, $P = 0.028$), 72-hour cumulative fluid balance after admission (5727.5 vs. 3041.0 ml, $P = 0.006$), and length of hospital stay (57.0 vs. 25.0 days, $P < 0.001$). Patients in the failure group had more Hetastarch injected during surgery (1000.0, IQR 1000.0-1500.0 ml) than those in the successful group (1000.0, IQR 500.0-1000.0 ml, $P = 0.015$) (Table 2).

Furthermore, the failure group had lower median values of red blood cell (RBC) count (2.8 vs. 3.3 × 10^{12}/L, $P = 0.022$), platelet count (103.0 vs. 162.5 × 10^{9}/L, $P = 0.014$), and albumin (25.8 vs. 32.7 g/L, $P = 0.002$) measured immediately after surgery (Table 2). No significant difference was observed in the length of ICU stay or other laboratory findings (Table S1 in Additional file 1).

Predictors and risk factors for replantation failure

All patients underwent laboratory examinations after admission and surgery. The AUCs and cutoff values of each single index are shown in Table S2 (Additional file 1). Combined predictors were selected according to the AUC, sensitivity, and specificity of each index. The results of the joint prediction analysis are presented in Table S3 (Additional file 1). We found that three factors (lactic acid on admission, 72 h cumulative fluid balance, and albumin level immediately postoperatively) and their combined prediction showed predictive power for replantation failure (Fig. 2). The lactic acid cutoff on admission was 1.55 mmol/l with an AUC of 0.692 (95% confidence interval, 0.549–0.835; $P = 0.017$), a sensitivity of 68.8%, and a specificity of 72.2%. The 72 h cumulative fluid balance cutoff was 4885.6 ml with an AUC of 0.755

(95% CI, 0.600-0.911; $P = 0.006$), a sensitivity of 66.7%, and a specificity of 84.5%. The immediate postoperative albumin level cutoff was 26.75 g/L with an AUC of 0.751 (95% CI, 0.631–0.871; $P = 0.002$), a sensitivity of 63.8%, and a specificity of 94.1%. The AUC of joint prediction was 0.838 (95% CI, 0.722–0.954; $P < 0.001$) with a sensitivity of 89.7% and a specificity of 69.2%.

Univariate logistic regression analysis showed that lower limb trauma, MESS, lactic acid on admission, RBC count immediately after surgery, platelet count after surgery, albumin level after surgery, volume of hetastarch injection during surgery, and 72 h cumulative fluid balance after admission were significantly associated with limb necrosis after replantation (Table S4 in Additional file 1). Multivariable logistic regression analysis found that lower limb trauma (odds ratio = 8.65, 95% CI 1.64–45.56, $P = 0.011$), MESS (odds ratio = 2.24, 95% CI 1.25–4.01, $P = 0.007$), and first 72 h cumulative fluid balance > 4885.6 ml (odds ratio = 10.25, 95% CI 1.37–76.93, $P = 0.024$) were independent risk factors for replantation failure (Fig. 3).

Discussion

Patients who had replantation failure needed to undergo at least one additional surgery (including amputation) and had a longer length of hospital stay [4, 15]. These conditions can lead to increased physical, psychosocial, and economic burdens on patients [4, 18]. Exploring risk factors or predictors of replantation failure may have clinical value for replantation management. In this retrospective study of patients with severe traumatic major limb mutilation who had replantation, we found that lactic acid on admission, 72 h cumulative fluid balance, and albumin level taken immediately post-operation, and their joint prediction showed significant predictive power for replantation failure. Moreover, lower limb trauma, MESS, and first 72 h cumulative fluid balance > 4885.6 ml were independently associated with replantation failure.

In this study, the failure rate of replantation was as high as 72.7%, and the delayed amputation rate was 10.6%. These results were similar to those of previous studies, which reported that the amputation rate of blunt arterial trauma of the limbs was 28–71%, and the delayed amputation rate was 11.7% [17, 19]. Higher injury severity, blunt trauma, location of trauma, and absence of pulses may be associated with failure [8]. All the patients were in critical condition in our cohort, almost all of whom had blunt trauma accompanied by discontinuous vessels, nerves, muscles, and bone structures to varying degrees. High energy transfer from blunt injury has been noted to cause extensive damage to associated soft tissue, bone, and nerves [19–21], and this mechanism may be a potential cause of poor outcomes in this cohort.

Major limb mutilation is often accompanied by severe blood loss such that good perfusion is essential for graft survival [22]. Even mild preoperative anemia was associated with an increased risk of wounds, sepsis, and thromboembolic complications in patients undergoing major non-cardiac surgery [23]. Blood loss can result in oxygen delivery (DO_2) reduction sufficient to cause tissue ischemia. Lactic acid may be helpful in predicting levels of oxygen debt accumulation and resuscitation needs, and its measurement may serve as a predictor of high-risk trauma [24]. Central venous oxygen saturation as another indicator of tissue oxygenation may be valuable for predicting the prognosis of large limb replantation [25]. Lactic

acid and albumin levels were found to be good predictors of replantation failure in this study. The wound healing time of rats in the continuous protein-free diet group was significantly prolonged [26]. Malnutrition is an independent risk factor for infection and wound complications after lumbar fusion and is associated with a longer hospital stay [27]. These common laboratory indicators should be considered during diagnosis and treatment.

Our results showed that the cumulative fluid balance had high sensitivity and good predictive ability. Fluid accumulation may lead to hemodilution, decreased perfusion pressure gradient due to elevated venous pressure, and inhibited oxygen diffusion between capillaries and cells due to interstitial edema [28]. Microcirculatory hypoperfusion and organ ischemia-reperfusion injury are related to prolonged liquid administration time [29]. Reperfusion injury after replantation can lead to irreversible damage, which can activate complement, cytokines, and chemokines, resulting in cell, membrane, and microvascular damage that impairs outcomes [22]. This may partly explain the independent association between excessive fluid involvement and replantation failure.

Restoring tissue perfusion may be critical for successful limb salvage [13]. Of the tissues involved in major limb trauma, muscles are the least resistant to ischemia [30]. Compared with the lower limbs, the upper extremities have less muscle mass, and an increase in collateral circulation may prolong the reperfusion time [31–33]. Anatomic and functional differences make the upper extremities more receptive to limb salvage and/or replantation than the lower limbs [34]. Additionally, the MESS evaluates limb trauma by integrating the extent of bone and soft tissue injury, limb ischemia, shock, and age [4]. Higher MESS increased the risk of delayed amputations. However, despite the high scores, limb salvage was successful in many patients [8]. Although MESS did not have a good sensitivity in predicting replantation failure in this study, it was indeed an independent risk factor. MESS may help quantify the overall severity of limb injury [8]. This highlights the need for MESS evaluation prior to treatment.

Because of the limitations of its retrospective nature, this study could not obtain the details of trauma completely and could not evaluate the recovery of limb function of the patients. In the joint predictive analysis, the cutoff values of each single index could not be obtained. However, these indexes should still be considered in the traumatic mutilation of major limbs. Due to the small sample size, more prospective studies are needed to further analyze the potential predictors.

Conclusion

Lower limb trauma, MESS, and 72 h cumulative fluid balance were associated with replantation failure. This implies the importance of fluid management in achieving major limb salvage. The joint predictors of lactic acid, cumulative fluid balance, and albumin showed a significant predictive power for replantation failure. More studies are needed to explore the predictive power of indicators related to tissue oxygenation and wound healing for replantation failure.

Abbreviations

MESS: mangled extremity severity scores

IQR: interquartile range

ROC: Receiver operating characteristic

AUC: area under the curve

VSD: vacuum sealing drainage

RBC: red blood cell

DO2: oxygen delivery

Declarations

Ethics approval and consent to participate

This study was approved by the Institutional Review Boards of the Suzhou Ruixing Medical Group (2021023).

Consent for publication

All authors agree to publish.

Availability of data

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

QG and RH conceived and designed the study, managed the data in the study, and took responsibility for the integrity of the data and the accuracy of the data analysis. CG performed the statistical analyses. CG, LY, and JJ drafted the manuscript. CG, MW, KZ, XL and LY collected the data. QG contributed to critical revision of the report. All authors contributed to data acquisition, data analysis, or data interpretation, and reviewed and approved the final version.

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Figures

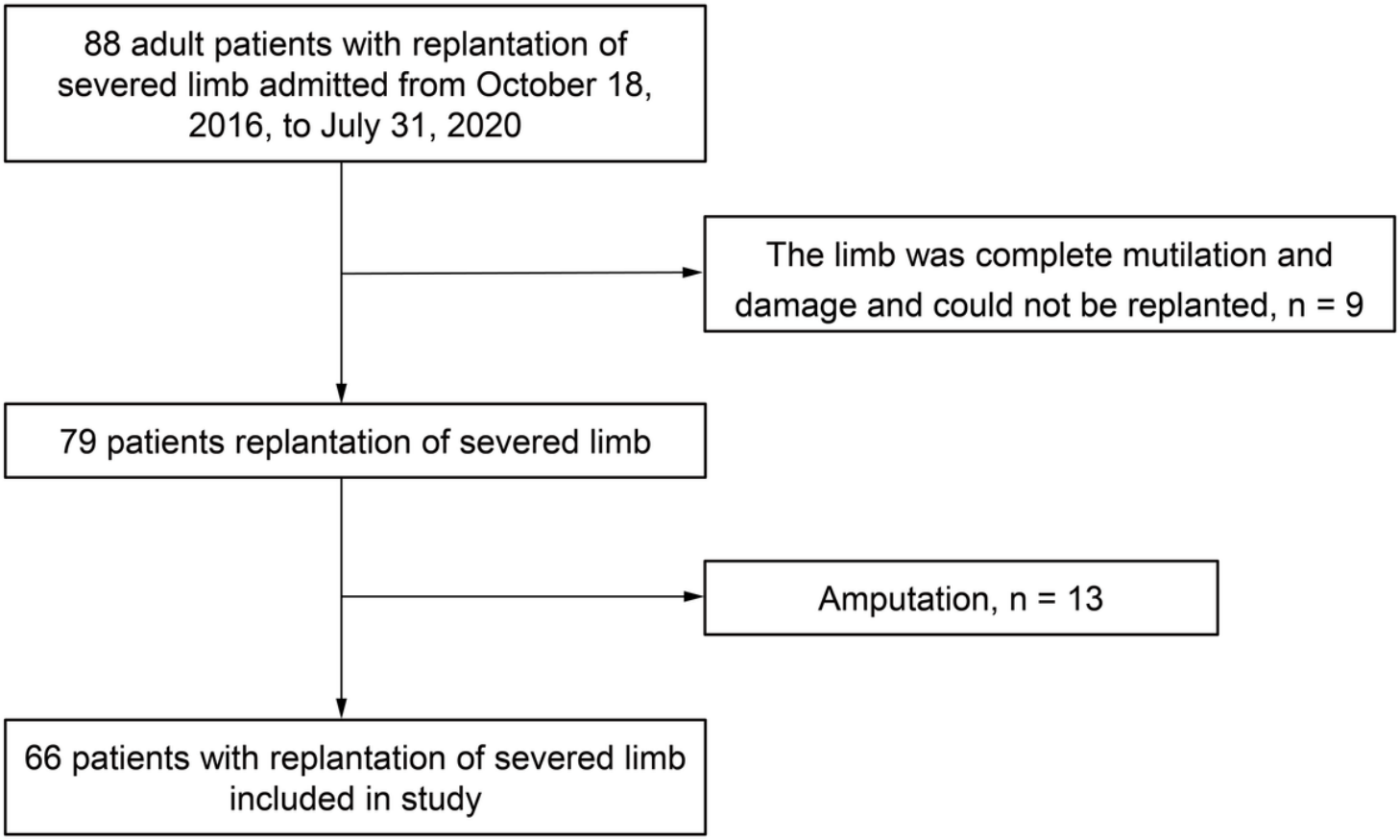
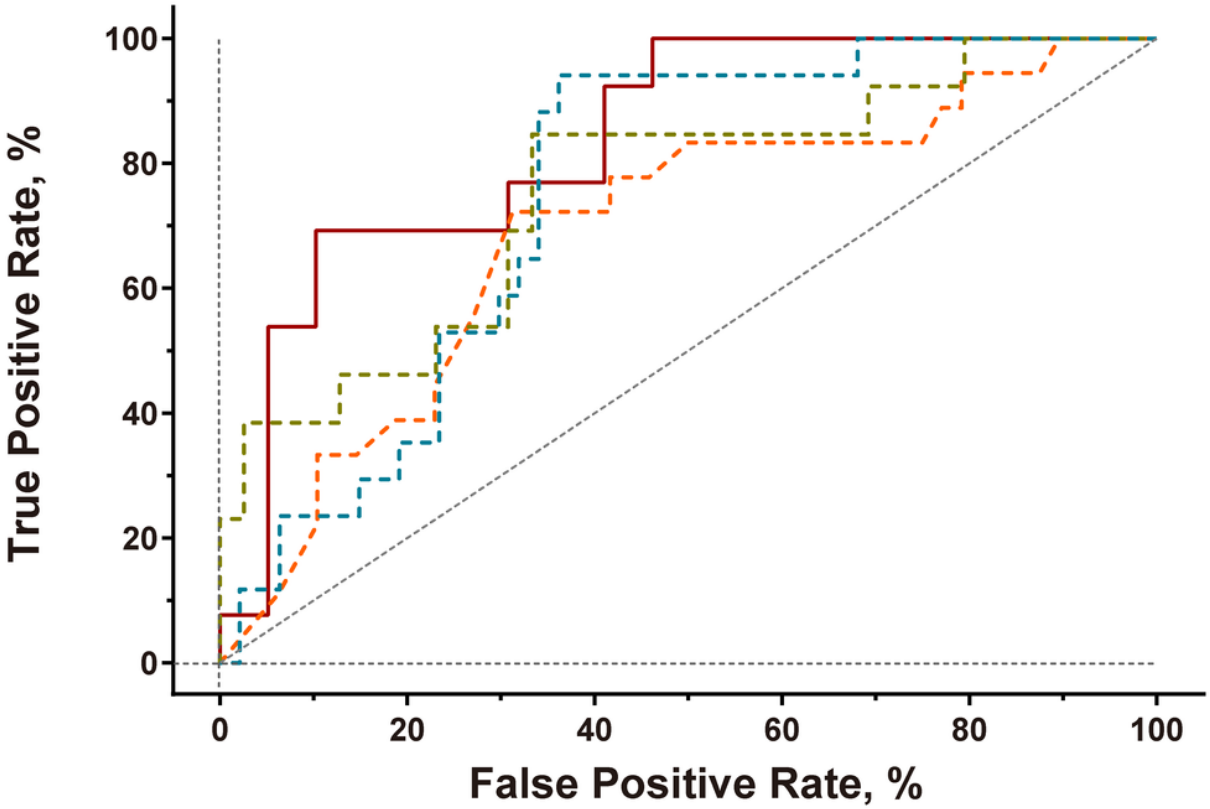


Figure 1

Study flowchart.



Factors	AUC	95%CI	Sensitivity	Specificity	P	Cut off value
Lactic acid	0.692	0.549-0.835	0.688	0.722	0.017	1.55
72h cumulative fluid balance	0.755	0.600-0.911	0.667	0.845	0.006	4885.6
Albumin	0.751	0.631-0.871	0.638	0.941	0.002	26.75
Joint prediction	0.838	0.722-0.954	0.897	0.692	<0.001	-

Figure 2

Combined indicators predict replantation failure. Lactic acid was measured on admission. Albumin level was measured after surgery immediately. Cutoff value was obtained through ROC analysis of each indicator.

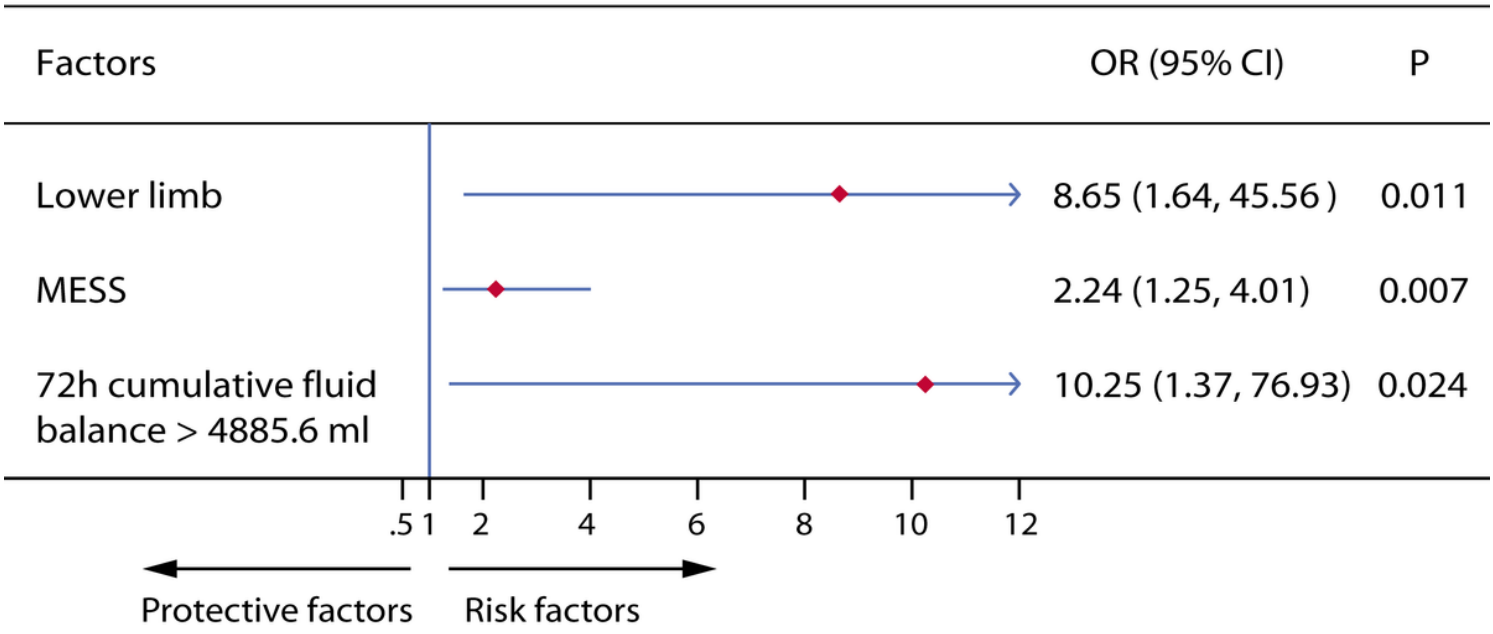


Figure 3

Multivariate logistic analysis of factors associated with replantation failure in 66 patients.

Supplementary Files

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