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A Meta-analysis of the Risk Factors for the Failure of Free Flap Transplantation

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Abstract: Objective: To systematically analyze the risk factors of free flap failure. Method: To retrieve the literature pertaining to the study of risk factors for the failure of free flap transplantation published prior to November 10, 2022, the following databases were searched: Pubmed, Web Of Science, Embase, Medline, CNKI, Wanfang, and CBM. The included and excluded criteria were applied to screen the literature that met the standards. The Newcastle-Ottawa Scale (NOS) was utilized to assess the quality of the included studies, and the RevMan 5.4 software was employed to conduct the meta-analysis of the included literature. Result: Among the 14 included studies, encompassing a total of 32,325 subjects, the following 16 risk factors were identified as contributors to the failure of free flap transplantation: body mass index (BMI) (OR = 1.81, 95% CI [1.10, 2.98]), smoking history (OR = 1.58, 95% CI [1.02, 2.45]), diabetes (OR = 1.92, 95% CI [1.04, 3.56]), hypertension (OR = 1.41, 95% CI [1.01, 1.97]), ASA score (OR = 0.62, 95% CI [0.46, 0.84]), surgical duration (OR = 0.47, 95% CI [0.09, 0.86]), intraoperative blood loss (OR = 0.21, 95% CI [0.08, 0.54]), and artery-to-vein ratio (OR = 3.71, 95% CI [2.00, 6.89]). These factors significantly influence the likelihood of transplant failure in free flap transplantation patients. Conclusion: The general condition, medical history, and treatment of patients undergoing free flap transplantation can all potentially impact the occurrence of surgical failure. It is crucial in clinical practice to accurately identify individuals at high risk for free flap transplantation and promptly intervene to address relevant risk factors, thus enhancing the overall surgical outcomes.

Keywords: Flap; Free flap transplantation; Risk factors; Meta-analysis

1. Introduction

Flap transplantation and reconstructive surgery have become routine procedures for the restoration of defects in the head and neck, breast, trunk, and limbs. The occurrence of failed free flap transplantation still persists in clinical practice. Such failures not only cause physical and psychological distress to patients and impose financial burdens on their families but also result in the wastage of medical resources. Therefore, it is imperative to explore the risk factors influencing the failure of free flap transplantation as a means to prevent such failures and enhance clinical outcomes.

2. Materials and methods

2.1 The search strategy and databases

We conducted a literature search in computer databases including Pubmed, Web of Science, Embase, Medline, CNKI, Wanfang, and CBMdisc for studies published before November 10, 2022, on the risk factors associated with failed free flap transplantation. We used a combination of controlled vocabulary and free-text terms as part of our search strategy. The retrieved literature was screened based on predefined inclusion and exclusion criteria. The selected studies that met the evaluation criteria were subjected to meta-analysis using RevMan 5.4 software. The search terms used were “Free flap”,”failure/dead”,”Risk factors”,”Influence factors” or “relevant factors”.

2.2 Inclusion and exclusion criteria

Inclusion criteria: ①Published studies on the risk factors associated with failed free flap transplantation, both domestically and internationally.②Study types include prospective or retrospective cohort studies.③Original articles or studies with calculated odds ratios (OR) and their corresponding 95% confidence intervals (CI).④Outcome measures include flap necrosis within 30 days after

transplantation or the need for flap salvage after transplantation. Exclusion criteria: ①Duplicate publications, reviews, and systematic reviews.②Studies deemed to have inadequate quality by the researchers.③Literature with incomplete data or flawed study designs.

2.3 Literature screening and data extraction

All literature was imported into Endnote X9 software and two researchers independently conducted literature screening and data extraction based on the inclusion and exclusion criteria. The extracted data included the first author, publication date, country, study type, study period, recipient site, total number of cases, number of flaps, number of failed transplants, and risk factors, which were cross-checked for accuracy.

2.4 Assessment of literature quality

Two researchers independently assessed the quality of the included studies using the Newcastle-Ottawa Scale (NOS). The assessment criteria included selection of study participants (4 points), comparability between groups (2 points), and outcome measurement (3 points), with a total score ranging from 0 to 9. An article with a score of ≥6 was considered to have high quality and classified as Grade A, while an article with a score of <6 was considered to have low quality and classified as Grade B. In case of any disagreements, a third researcher was consulted for resolution.

2.5 Statistical methods

The statistical analysis of the included studies was performed using RevMan 5.4 software. Heterogeneity among the studies was assessed using the chi-square test, where a $P > 0.1$ and $I^2 \leq 50\%$ indicated high homogeneity and a fixed-effects model was used for analysis. A $P \leq 0.1$ and $I^2 > 50\%$ indicated statistical heterogeneity in the literature. In such cases, after excluding clinical and methodological heterogeneity as potential sources, a random-effects model was used for analysis. Sensitivity analyses were conducted by comparing the results obtained from the fixed-effects model and random-effects model.

3. Result

3.1 Results of literature screening

A total of 1025 articles were initially retrieved through the search, and after the repeated screening, 14 articles were included, with a total of 32,325 study subjects.

3.2 Assessment of the quality of included literature

Among the 14 included articles, 9 received a quality score of 7, and 5 received a score of 6. Overall, the quality of the literature was high, as shown in Table 1.

3.3 Meta-analysis results

For risk factors with homogeneity ($P > 0.1$, $I^2 \leq 50\%$), a fixed-effects model was used to analyze the data from the included studies. While risk factors with heterogeneity ($P \leq 0.1$, $I^2 > 50\%$), a random-effects model was employed for analysis. The following risk factors demonstrated statistically significant combined effect sizes ($P < 0.05$): body mass index, smoking history, hypertension, diabetes, ASA score, surgical duration, intraoperative blood transfusion volume, and artery-to-vein anastomosis ratio. However, the combined effect sizes of age, gender, alcohol consumption history, peripheral vascular diseases, defect area, preoperative radiotherapy, and arterial anastomosis method did not reach statistical significance ($P \geq 0.05$), as shown in Table 2.

4. Discussion

4.1 General risk factors

The study conducted by Kwok, A. C. et al. demonstrated that patients with a BMI exceeding the normal range or who are obese have a higher risk of experiencing failed free flap transplantation compared to patients with a normal body mass index[1]. It has been suggested by studies that obese patients may have excessively thick free flaps, which can lead to compression within narrow spaces, resulting in compromised venous outflow and inadequate blood supply to the transplanted tissue[2]. This increases the risk of tissue necrosis. Therefore, researchers recommend that for free flap transplantation in obese patients, thinner flaps such as forearm flaps should be selected, or thick flaps should be thinned through appropriate techniques. Smoking is a risk factor that can significantly impact the survival of flap transplants. Nicotine, present in tobacco, has a stimulatory effect that causes vasoconstriction, leading to reduced blood supply to the recipient site. As a result, the transplanted flap may not receive sufficient oxygen and nutrients[3]. Therefore, it is crucial to inform patients about the detrimental effects of smoking on flap transplantation during the perioperative period.

4.2 Disease-related factors

Studies have indicated that systemic underlying diseases, such as diabetes and peripheral vascular diseases, can decrease the sur-

vival rate of free flaps and increase the incidence of postoperative complications. Diabetes can lead to outcomes such as endothelial damage, decreased vascular elasticity, and layered anastomotic vessels. In a retrospective study conducted by Rosado et al., involving 7,890 patients who underwent microsurgical reconstruction of the head and neck, it was found that the incidence of diabetes was 2.3 times higher in patients who experienced free flap failure compared to those who had successful free flap transfer[4].

4.3 Treatment-related factors

Ishimaru et al. found a significant increase in free flap failure associated with longer surgical duration[5]. Additionally, in a study conducted by Sanati Mehrizy et al. univariate analysis revealed an association between flap failure and surgical duration. Prolonged surgical duration typically implies longer ischemic and hypoxic injury, leading to tissue damage[6]. The ischemic time of the flap may serve as a better indicator for predicting flap outcomes. This study found that the number of venous anastomoses in flap transplantation is a risk factor for flap transplantation failure, which is consistent with the findings of other studies. Some researchers suggest that if a free flap has two or more veins, it is preferable to perform simultaneous anastomosis of multiple veins, as this can reduce the rate of flap necrosis[7]. Additionally, postoperative factors such as monitoring protocols, anticoagulation therapy, and surgical interventions may also influence the outcomes of free flaps.

5. Conclusion:

The general condition, medical history, and treatment of patients undergoing free flap transplantation can all potentially impact the occurrence of surgical failure. It is crucial in clinical practice to accurately identify individuals at high risk for free flap transplantation and promptly intervene to address relevant risk factors, thus enhancing the overall surgical outcomes.

Table 1 Evaluation of the quality of the included

Inclouded papers	Selection of study subjects (point)	Comparabilitybe tween groups (point)	Measurement of exposure factors (point)	NOS (point)	Quality grade
Wong,A.K.2015	3	2	2	7	A
Cho, E. H.2015	3	2	2	7	A
Xiaowei Peng2015	3	2	2	7	A
ZhigangYu.2016	3	2	2	7	A
Ishimaru,M.2016	3	2	2	7	A
Mucke, T.2016	2	2	2	6	A
Sanati.Mehrizy,P.2016	3	2	2	7	A
Kwok, A. C.2017	3	2	2	7	A
Zhou, W.2017	2	2	2	6	A
Yang, X. Q.2018	2	2	2	6	A
Wang, K. Y.2019	3	2	2	7	A
Lin, Y.2019	3	2	2	7	A
Othman, S.2021	2	2	2	6	A
Lese, I.2021	2	2	2	6	A

Note: NOS —Newcastle-Otawa Scale

References:

[1] Kwok A C, Agarwal J P. An analysis of free flap failure using the ACS NSQIP database. Does flap site and flap type matter? [J]. Microsurgery, 2017, 37(6) : 531-8.

[2] Analysis of the causes of flap necrosis after head and neck reconstruction [J].Chin J of Otorhinolaryngology Head and Neck Surg,2015(2)

[3] Lese I, Biedermann R, Constantinescu M, et al. Predicting risk factors that lead to free flap failure and vascular compromise: A single unit experience with 565 free tissue transfers [J]. Journal of plastic, reconstructive & aesthetic surgery : JPRAS, 2021, 74(3)

Table 2 Meta-analysis outcome included papers

Risk factors	Number of papers	Heterogeneity test P	Heterogeneity test I^2	Model	OR/ SMD	95%CI	P
General factors							
Age	5	0.18	36%	b	0.77	[0.56, 1.05]	0.1
Gender	10	0.58	0	b	1.08	[0.86, 1.37]	0.5
BMI	7	0.004	69%	a	1.81	[1.10, 2.98]	0.02
Somking	10	0.0003	71%	a	1.58	[1.02, 2.45]	0.04
Drinking	3	0.002	84%	a	1.86	[0.26, 13.11]	0.53
Disease-related factors							
Hypertension	5	0.84	0	b	1.41	[1.01, 1.97]	0.04
Diabetes	10	<0.00001	78%	a	1.92	[1.04, 3.56]	0.04
Peripheral vascular disease	3	0.009	79%	a	4.29	[0.99, 18.60]	0.05
ASA Score	5	0.91	0	b	0.62	[0.46, 0.84]	0.002
Defect size	2	0.33	0	b	0.19	[-0.88, 0.46]	0.17
Defect etiology	2	<0.00001	86%	a	1.45	[0.55, 3.84]	0.45
Treatment-related factors							
Preoperative radiotherapy	4	0.001	81%	a	0.93	[0.31, 2.78]	0.9
Operative time	4	0.007	75%	a	0.47	[0.09, 0.86]	0.001
Number of RBC units transfused	2	0.34	0	b	0.21	[0.08, 0.54]	0.001
Arteriovenous ratio	3	0.95	0	b	3.71	[2.00, 6.89]	<0.0001
Arterial anastomosis	2	0.4	0	b	1.44	[0.78, 2.66]	0.24

Note: CI—Confidential interval; a: Random Model, b: Fixed Model.

: 512-22.

[4] Rosado P, Cheng H T, Wu C M, et al. Influence of diabetes mellitus on postoperative complications and failure in head and neck free flap reconstruction: a systematic review and meta-analysis [J]. Head & neck, 2015, 37(4) : 615-8.

[5] Ishimaru M, Ono S, Suzuki S, et al. Risk Factors for Free Flap Failure in 2,846 Patients With Head and Neck Cancer: A National Database Study in Japan [J]. J Oral Maxillofac Surg, 2016, 74(6) : 1265-70.

[6] Sanati-Mehrizy P, Massenburg B B, Rozehnal J M, et al. Risk Factors Leading to Free Flap Failure: Analysis From the National Surgical Quality Improvement Program Database [J]. J Craniofac Surg, 2016, 27(8) : 1956-64.

[7] Analysis of the risk factors of free flaps necrosis used for reconstruction of head-neck defects[J].J Clinical Stomatology,2016,32(11) :681-4.