# A Meta-analysis Study : Risk Factors of Total Flap Necrosis in Microsurgery

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**Abstract**

**Background:**
Free flap surgery allows closure of the defect with excellent results. Developed knowledge and skills lead to higher success rates. Failure to do so in the form of total flap necrosis can cause burdensome problems for both the surgeon and the patient. We performed a meta-analysis to analyze several risk factors for total flap necrosis in free flap surgery. Age, gender, diabetes mellitus (DM), hypertension (HT), duration of surgery, blood transfusions, and intraoperative intravenous fluids are among them.

**Methods:**
This study was prepared using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flowchart. We used the PubMed, Science Direct, Proquest, and Web of Science databases from January 2019 to December 2020. The selected articles described free flaps and included the number of cases according to variables and the incidence of total flap necrosis.

**Results:**
We found thirteen articles met the criteria for meta-analysis. A total of 2,063 free flaps were documented, and 65.9% were male patients. Most of the defects were caused by malignancies (75.4%). The most common location was the head and neck (72.7%). Free flaps from the lateral circumflex femoral system and the radial forearm are the two most common types of free flaps. The overall success of the free flap in this study was 93.45%, while the failure rate was 6.55%. Total necrosis was found in 23% of all postoperative complications. There were no significant differences in criteria for old age (> 60 years), female gender, DM, HT, and duration of surgery. Transfusions or intraoperative fluid administration cannot be concluded from this research.

**Conclusion:**
The causes of free flap failure are multifactorial and no absolute contraindications to surgery are mentioned in the literature. Some of the factors analyzed in this study were not significant as the risk of total free flap necrosis but could lead to other surgical or medical complications. However, further studies are needed.

Keywords : Free flap necrosis; free flap failure; free flap meta-analysis

## 1. Introduction

Free flap allows reconstruction at a distant recipient site, with local and regional tissue limitations and the need for specific tissue components that are missing. Free flap is a one-stage procedure, that makes postoperative recovery faster due to good vascularization of the new flap tissue. Donor closure can be performed on a primary basis to minimize morbidity.[1] It is very important to perform free flap surgery with available facilities and technical expertise. Specific trained surgeons and assistants are needed, particularly to share the workload of operations. Early times the chances of failure can reach 40-50 percent, and nowadays the success rate also increases as the techniques improves.[2] Nevertheless flap loss is still a huge burden for both surgeons and patients. In the postoperative period, it is imperative to recognize complications immediately and take salvaging measures before flap failure occurs. Therefore, it is prudent to better understand what causes free flaps to fail so that these events can be prevented. There are several factors that are thought to play roles in free flap success. Patient factors such as age, gender, comorbidities, smoking, history of radiotherapy in cases of malignancy, and presence of anemia can be assessed before surgery. Several surgical-related factors such as duration of surgery, number of perforators, and pedicle skeletonization are noteworthy. Studying the perioperative management of the anesthetic side, such as the anesthetic agent used, intraoperative fluid administration, and temperature, is interesting when determining the outcome of flaps.[3]

In this study, a systematic literature review and meta-analysis of existing studies will be carried out to explore the effect of the correlation between some risk factors and the incidence of free flap complications resulting in failure or total necrosis. This study was conducted during the Covid-19 pandemic.

## 2. Materials and Methods

This study is a meta-analysis study to determine the risk factors and their correlation to total flap necrosis. The independent variables were age, gender, diabetes mellitus, hypertension, duration of surgery, blood transfusion, and intraoperative fluids. The dependent variable was the total flap necrosis to represent failure of the free flap. Data on patients who underwent free flaps were collected with various etiologies and locations. The data was taken based on a literature search on the internet database in the period 2019 – 2020. The included studies can be retrospective, randomized controlled trials (RCTs), or prospective studies which include information about age, gender, comorbidities (diabetes mellitus and hypertension), duration of surgery, administration of transfusions and intraoperative fluids and complications that occur. All manuscripts are full-text accessible.

The data sources were obtained through four databases: PubMed, Science Direct, Proquest, and Web of Science. The literature search was determined using these keywords: (free flap[MeSH Terms]) AND (hypertension[MeSH Terms]), ("Free Tissue Flaps"[Mesh]) AND "diabetes mellitus"[Mesh], ("Operative Time"[Mesh]) AND "Free Tissue Flaps"[Mesh], (blood transfusion[MeSH Terms]) AND (free flap[MeSH Terms]), blood transfusion AND free flap, (intraoperative fluid) AND (free flap[MeSH Terms]). The search was limited to literature in English. Manual searches for unpublished reviews or studies were not conducted.

The studies that will be included in the meta-analysis are selected according to the PRISMA flowchart. Primary screening was carried out by one of the authors. Eligible articles are selected and read in full by two authors. Journals collected from search results and qualified go through a quality assessment using critical appraisal skills program (CASP).[4] The summary is made in a tabular format containing the author's name, year, design, number of samples, variables and outcomes. Using these journals, we analyzed the number of cases in each variable group, the number of flap losses, and the total number of operations. The same information is also provided for non-variable groups. Risk ratios are calculated based on this information.

### Statistical Analysis

The fixed-effects model and the random-effects model were used to combine several studies when the sample sizes were not the same. The I Square (I2) statistical test was used to assess heterogeneity. The software used to perform the meta-analysis is Review Manager version 5.4. Funnel plots were used to view the distribution of articles that were combined in the meta-analysis. The effect size value of each study is displayed in the form of a forest plot.[5] Summary effects of the meta-analysis are reported in the form of diamonds located at the lower end of the forest plot.

## 3. Results

The search results for each variable were 10,697 articles. After the duplicate titles and authors were removed, 5,476 articles were obtained. A total of 304 articles were excluded with languages other than English, animal studies, irrelevant topics, incomplete and inaccessible data. In the end, thirteen articles met the criteria for meta-analysis.

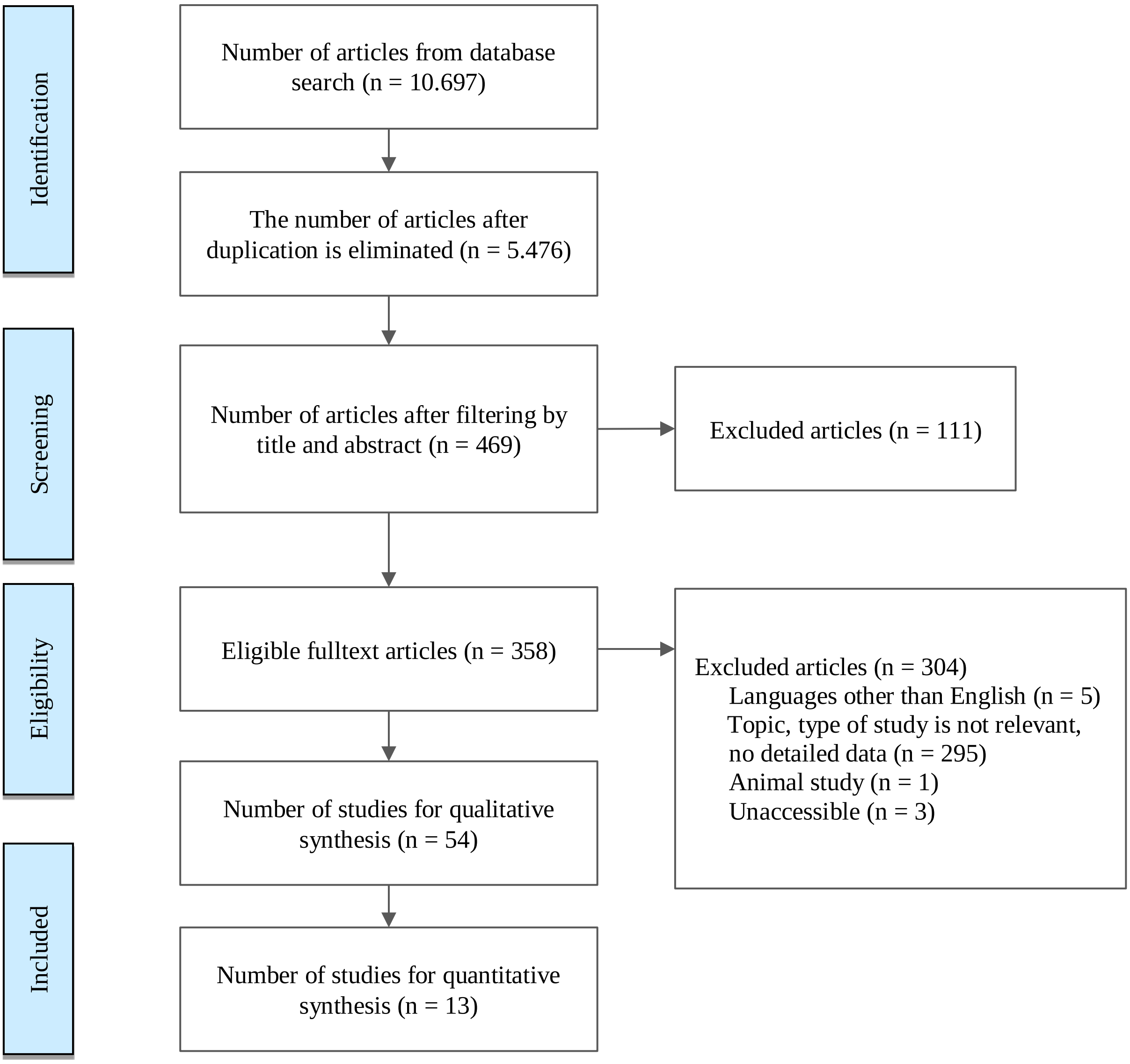


Fig. 1. PRISMA flowchart

3.1 Study demographics

The studies included in this meta-analysis originated from various countries in Europe, America, Asia and Africa. Most studies car and the United States (31%, 4 studies each). Another study came from Asia at about 15% (2 studies from Japan and China). The rest (South America), Turkey (Asia-Europe), and Egypt (Asia-Africa) each study (8%). The data is shown in table 1. From these 13 stud of patients was 2,049 people, and the number of cases treated was 2,063 free flaps. Of these patients, the majority were male as many (65.9%), and women as many as 699 people (34.1%). The average age was 43 years, with an age range of 8-93 years.

Table 1. Overview of meta-analysis

| Study | Country | Study type | Number of free flap | Number of patients | Age (mean) | Free Flap Type | Complications |
|---|---|---|---|---|---|---|---|
| Caliceti et al., 2019 | Italy | Retrospective | 21 | 21 | 59,1 | ALT 100% (n = 21) | Partial necrosis 9,52 % (n = 2), total necrosis 4,76 % (n = 1) |
| Crawley et al., 2019 | United States | Retrospective | 892 | 892 | 59,95 | ALT 45,9% (n = 410), Fibular 21,1% (n=189), RFF 25,89% (n=231), Lattisimus & scapula 5,94% (n=53), flap lain 1% (n=9) | Total necrosis 4,8%% (n = 43) |
| Deldar et al., 2020 | United States | Retrospective | 7 | 6 | 68,4 | ALT 71,4% (n=5), VL 14,3% (n=1), Lattisimus 14,3% (n=1) | dehiscence 14,2% (n = 1) |
| Ekin et al., 2019 | Turkey | Retrospective | 77 | 77 | 49,3 | ALT 10,4% (n=8), Fibular 25,9% (n=20), RFF 12,9% (n=10), Lattisimus 2,59% (n=2), DIEP 48% (n=37) | Hematoma 10,4 % (n =8), dehiscence 7,8 % (n =6), thrombosis 6,5 % (n =5), partial necrosis 5,2% (n = 4), total necrosis 3,89% (n = 3) |

| **Study** | **Country** | **Study type** | **Number of free flap** | **Number of patients** | **Age (mean)** | **Free Flap Type** | **Complications** |
|---|---|---|---|---|---|---|---|
| Heidekrueger et al., 2019 | Germany | Retrospective | 100 | 89 | 54,3 | ALT 46% (n=46), Gracillis 54% (n=54) | Hematom 6% (n=6), thrombosis 13% (n=13), partial necrosis 6% (n=6), total necrosis 9% (n=9) |
| Lee et al., 2020 | United States | Retrospective | 33 | 33 | 54 | ALT 3% (n=1), RFF 12,1% (n=4), lattisimus & scapula 16,8% (n=13), gracilis 3% (n=1), rectus 30 % (n=10) | Hematoma 9% (n =3), dehiscence 18,18 % (n = 6), thrombosis 9% (n =3), partial necrosis 12,12 % (n = 4), total necrosis 9 % (n = 3) |
| Lese et al., 2020 | Switzerland | Retrospective | 565 | 565 | 50,68 | ALT 32,38% (n=183), RFF 13,27% (n=75), lattisimus & scapula 22,12% (n=125), gracilis 13,9% (n=79), DIEP 7 % (n=40), flap lain 3,36% (n=19) | Hematoma 9,2% (n =52), dehiscence 8,1% (n = 46), infection 9,9% (n = 56), partial necrosis 15,75 % (n = 89), total necrosis 3,19% (n = 18) |
| Manrique et al., 2020 | Peru | Retrospective | 34 | 34 | 52.64 | Ileocolon 100% (n=34) | Hematoma 2,9% (n =1), partial |

| Study | Country | Study type | Number of free flap | Number of patients | Age (mean) | Free Flap Type | Complications |
|---|---|---|---|---|---|---|---|
| | | | | | | | necrosis 5,88 % (n = 2), total necrosis 2,9% (n = 1) |
| Noaman et al., 2020 | Egypt | Retrospective | 15 | 15 | 29,6 | Fibular 100% (n=15) | total necrosis 13,3% (n = 2) |
| Othman et al., 2020 | United States | Retrospective | 18 | 16 | 70.5 | ALT 83,3% (n = 15), RFF 5,5 % (n=1), lattisimus 11,1% (n=2), flap lain 1% (n=9) | Hematoma 5,55% (n =1), dehiscence 22,2% (n = 4), infection 11,1% (n = 2), total necrosis 16,6% (n = 3) |
| Otsuki et al., 2020 | Japan | Retrospective | 13 | 13 | 82,6 | RFF 23% (n=3), Jejunum 7,69% (n=1) | |
| Wolfer et al., 2020 | Germany | Retrospective | 280 | 280 | 59,72 | Fibular 1,42% (n=4), RFF 50,7% (n=142), scapula-Lattisimus 43,9% (n=123), DIEP 48% (n=37) | partial necrosis 0,7% (n =2), total necrosis 5% (n = 14) |
| Zhang et al., 2020 | China | Retrospective | 8 | 8 | 38,2 | ALT 75% (n =6 ), lattisimus 12,5% (n=1), flap lain 12,5% (n=1) | total necrosis 12,5% (n = 1) |
| | Total | | 2063 | 2049 | 43,28 | | |

Table 2. Characteristic of Study

| Description | | Number of case (n) | Percentage (%) |
|---|---|---|---|
| Mean of age (year) | | 43,28 | |
| Gender | Men | 1351 | 65,9 |
| | Woman | 699 | 34,1 |
| | Total | 2050 | |
| Etiology | Cancer | 1502 | 75,4 |
| | Gunshot injury | 2 | 0,1 |
| | Non malignancy | 106 | 5,3 |
| | Osteomyelitis | 87 | 4,4 |
| | Chronic wound | 33 | 1,7 |
| | Vascular disease | 28 | 1,4 |
| | Total | 1992 | |
| Defect location | Head and neck | 1448 | 72,9 |
| | Lower extremity | 401 | 20,2 |
| | Trunk | 84 | 4,2 |
| | Upper extremity | 53 | 2,7 |
| | Total | 1986 | |
| Free Flap Type | Lateral Circumflex Femoral System (Anterolateral thigh perforator, vastus lateralis, anteromedial thigh perforator, femur) | 696 | 33,7 |
| | Radial Forearm | 403 | 19,5 |
| | Scapular & Subscapular System (Latissimus dorsi, parascapular, thoracodorsal perforator) | 320 | 15,5 |
| | Peroneal System (Fibula osteocutaneous, fibula osseous, peroneal perforator) | 303 | 14,7 |
| | Medial Circumflex Femoral System (Gracilis muscle) | 134 | 6,5 |
| | Inferior Epigastric System | 77 | 3,7 |
| | Rectus | 42 | 2,0 |
| | Jejunum | 10 | 0,5 |
| | Other flap | 78 | 3,8 |
| | Total | 2063 | |
| Comorbidity | Diabetes mellitus | 255 | 11,1 |
| | Hypertension | 632 | 29,0 |

Table 3. Complications

| Complications | Numbers (n) | Percentage (%) |
|---|---|---|
| Thrombosis | 77 | 3,7 |
| Hematoma | 71 | 3,4 |
| Dehiscence | 63 | 3,1 |
| Infection | 2 | 0,1 |
| Partial necrosis | 109 | 5,3 |
| Total necrosis | 98 | 4,8 |
| Total | 420 | 20 |

3.2 Meta-analysis of Risk Factors for Free Flap Failure

| Study or Subgroup | >= 60 Events | >= 60 Total | < 60 Events | < 60 Total | Weight | Risk Ratio M-H, Fixed, 95% CI |
|---|---|---|---|---|---|---|
| Caliceti 2019 | 0 | 10 | 1 | 11 | 56.8% | 0.36 [0.02, 8.03] |
| Ekin 2019 | 3 | 18 | 0 | 59 | 9.5% | 22.11 [1.19, 409.01] |
| Manrique 2019 | 0 | 2 | 1 | 32 | 9.9% | 3.67 [0.19, 71.78] |
| Zhang 2020 | 0 | 1 | 1 | 7 | 23.8% | 1.33 [0.08, 21.94] |
| **Total (95% CI)** | | **31** | | **109** | **100.0%** | **2.99 [0.98, 9.15]** |
| Total events | 3 | | 3 | | | |

Heterogeneity: Chi² = 3.92, df = 3 (P = 0.27); I² = 24%
Test for overall effect: Z = 1.92 (P = 0.05)

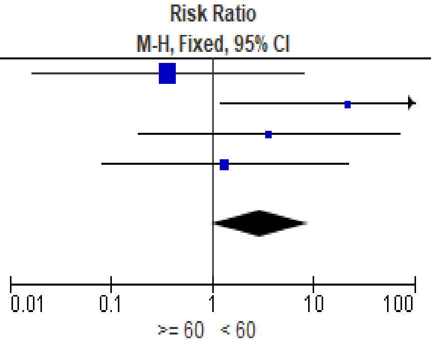


Figure 2. Free flap total necrosis risk analysis based on age

| Study or Subgroup | Male Events | Male Total | Female Events | Female Total | Weight | Risk Ratio M-H, Fixed, 95% CI |
|---|---|---|---|---|---|---|
| Caliceti 2019 | 1 | 15 | 0 | 6 | 1.3% | 1.31 [0.06, 28.41] |
| Crawley 2019 | 24 | 578 | 19 | 314 | 45.3% | 0.69 [0.38, 1.23] |
| Lee 2020 | 0 | 21 | 3 | 12 | 8.1% | 0.08 [0.00, 1.51] |
| Lese 2020 | 24 | 348 | 11 | 217 | 24.9% | 1.36 [0.68, 2.72] |
| Manrique 2019 | 1 | 29 | 0 | 5 | 1.5% | 0.60 [0.03, 13.03] |
| Noaman 2020 | 2 | 9 | 0 | 6 | 1.1% | 3.50 [0.20, 62.27] |
| Othman 2020 | 2 | 11 | 0 | 5 | 1.2% | 2.50 [0.14, 44.26] |
| Otsuki 2019 | 2 | 10 | 0 | 3 | 1.3% | 1.82 [0.11, 30.27] |
| Wolfer 2020 | 9 | 212 | 5 | 68 | 13.9% | 0.58 [0.20, 1.66] |
| Zhang 2020 | 1 | 6 | 0 | 2 | 1.3% | 1.29 [0.07, 23.39] |
| **Total (95% CI)** | | **1239** | | **638** | **100.0%** | **0.87 [0.60, 1.27]** |
| Total events | 66 | | 38 | | | |

Heterogeneity: Chi² = 7.19, df = 9 (P = 0.62); I² = 0%
Test for overall effect: Z = 0.72 (P = 0.47)

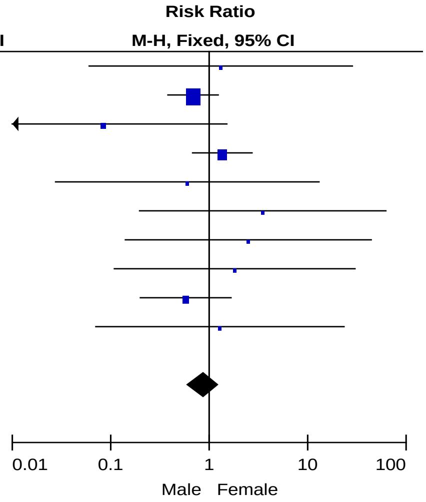


Figure 3. Gender risk analysis with total flap necrosis.

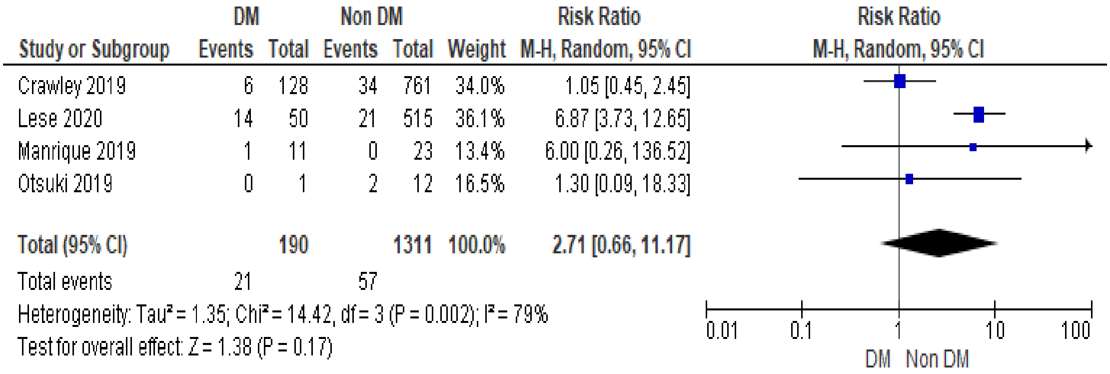


Figure 4. Relationship of diabetes mellitus risk with total flap necrosis

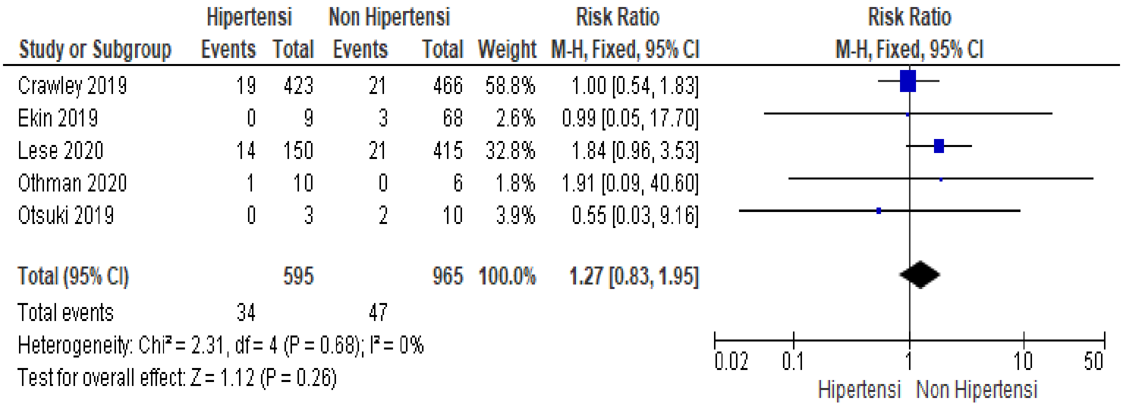


Figure 5. Analysis of risk factors for hypertension with total flap necrosis

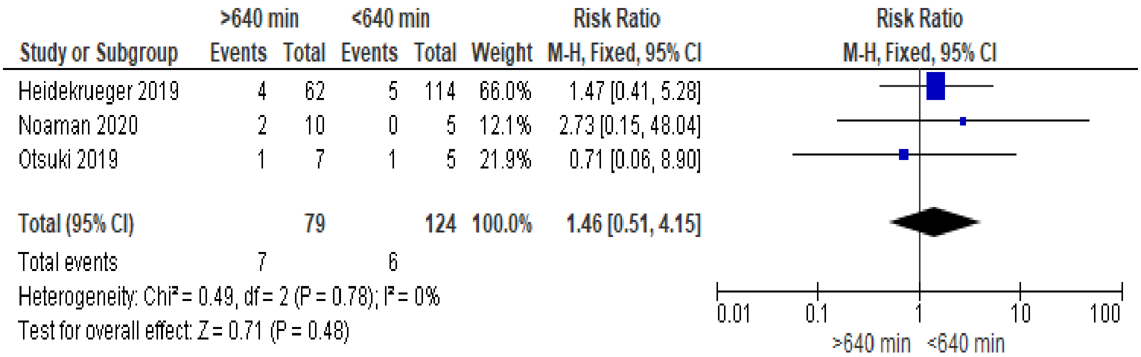


Figure 6. Forest plot analysis of risk factors for total flap necrosis based on duration of surgery

**Publication Bias**

No publication bias was found the meta-analysis of risk factor analysis based on age, gender, hypertension, operation duration. A meta-analytical study of comorbid DM, described a heterogeneous or randomized study.

## 4. Discussion

Patients who underwent free flaps came from all age categories from children to geriatrics, with an average adult age of 43 years (Table 1). Based on the summary of 13 studies, there were 2,063 cases of free flaps and a 1.9-fold higher proportion of males than females. The number of male patients was higher than female patients based on the textbook, but that relationship is not mentioned. The results of this study showed the most common etiology of defects was cancer or malignancy. Meanwhile, cancer incidence and mortality were found to be higher in men than women for all types of cancer affecting both genders.[6] A number of factors contribute to this, including lack of awareness of symptoms, lack of fruit and vegetable consumption, smoking and alcohol habit, and less frequent visits to health facilities by men.[7] Exposure to the work environment is another factor. Women have protective factors such as the estrogen and X chromosome.[8]

The most common defect locations that were closed with a free flap in this study were the head and neck area (table 2). Based on several studies from several other centers obtained variations. In the United States, multiple institutions reported that most free flap surgeries were performed in the breast area, followed by the head and neck.[9] Likewise, Kramer et al. wrote more free tissue transfer is performed for breast reconstruction.[10] Meanwhile, a study in Thailand [11] and in East Africa [12] declares the most recipient locations were the head and neck.

The most common types of free flaps used in this study were the anterolateral thigh (ALT) flap, radial forearm (RF) flap, lattisimus dorsi – scapular flap and fibular flap (table 2). Several types of these flaps are workhorse flaps for facial and extremity reconstruction.[13] The most common flaps for head and neck reconstruction are ALT, RF and fibular free flaps. Meanwhile, for breast reconstruction, a deep inferior epigastric perforator (DIEP) free flap is used.[10]

Based on this study, the success or survival of the free flap was 93.45% (table 1). In this study, the success rate was quite good which above 90%.[14] The most common postoperative complications were total necrosis (5.5%), followed by partial necrosis, thrombosis, hematoma, dehiscence and infection (table 3). Data from these 13 studies showed that the failure rate was 6.55%. There are some reports that the current failure rate is between 2 - 3 %. [1, 15]. However, according to Bank & Gottlieb, an expert in microsurgery can have a failure rate of up to 10% with a re-exploration rate of 16%.[16] It is therefore very important for the microsurgical team to prepare for the need to return to the operating room (takeback) during the postoperative period. All possibilities and outcomes of surgery should be discussed with the patient's family prior to surgery.

### 4.1 Free Flap Failure Risk Factors

Age

In the past, advanced age was said to be a contraindication to free flap surgery. This has slowly changed in the last few decades, as microsurgical techniques and instrumentation advances.[17] The results of four studies showed that there was no difference in the increased risk of those aged over 60 years and under 60 years for flap failure. The age limit used is 60 years in accordance with Law of The Republic of Indonesia No.13 of 1998 about Elderly Welfare, also adopting previous research by Qian, Y et al in 2016. Parsemain et al reported no significant difference in surgical complications in patients undergoing free flap over 70 years of age, compared with those under 70 years of age. Longer treatment times were found in the older age group, as well as postoperative medical complications.[18] There was no statistical significance of flap failure with age, but other conditions such as high ASA scores were associated with surgical complications.[19] Although chronological age itself does not directly relate to surgical complications, it is associated with medical complications, especially if many comorbidities are present.[20] Free flap reconstructive surgery should not only consider the patient's age, but also their overall medical condition. It is important to perform a careful preoperative assessment, prepare the patient for comorbid disease, and ensure proper postoperative monitoring. Both life-threatening medical complications such as heart failure, myocardial infarction, sepsis, pulmonary embolism or minor medical complications such as acute respiratory disease and urinary retention should be considered in postoperative care.[18]

Gender

Estrogen is one of the protective factors for vascular endothelial cells against cell apoptosis. In one study, the free flap failure rate in women with a median age of over 50 years with post-menopausal status was higher than in men. Women may have a smaller vascular diameter than men so that anastomoses will be more difficult.[21] In this study, there was no difference in the risk of flap failure between men and women. These results are similar to free-style flaps meta-analysis.[22] However, contradictory results were also obtained. Multivariate analysis showed that male sex was significantly associated with flap failure.[23] This difference may be due to sample differences between studies.

Diabetes mellitus

The success of the anastomosis is affected by healthy blood vessels of the appropriate caliber, and good flow with walls and vascular sheaths that are easily dissected. Diabetic patients have atherosclerosis which interferes with blood and oxygen flow. Atherosclerotic plaques trigger remodeling of the arterial lumen. In addition, there are multifactorial wound healing disorders, due to growth factor deficiency, impaired cellular function of glucose and peripheral ischemia due to microvascular disorders. One of the growth factors is platelet-derived growth factor (PDGF), which response is recognizing the site of injury and initiate healing.[24] These conditions can trigger vascular thrombosis [25] and affect wound healing for both recipient and donor after free flap surgery. Many studies report DM as a negative predictor of free flap outcome. Diabetes is closely associated with major complications such as flap failure and life-threatening conditions according to a retrospective study in Taiwan.[26] A meta-analysis study by Caputo et al also showed a significant risk between DM and free flap failure in head and neck cancer reconstruction.[27] On the other hand, not all studies support the same conclusion. This study concluded that DM was not significantly associated with free flap failure. Kantar et al. also reported that no significant relationship between DM and free flap failure. However, the incidence of surgical wound infection, dehiscence, and long treatment time were found to be more common in DM patients than without it.[28] Free flap is considered feasible and safe to perform on lower extremity defects with diabetes, with a success rate of 90.9%.[29]. Another study on free flap breast reconstruction showed that DM was not a significant predictor of flap failure.[30] Despite the conflicting results found in various studies, DM remains a concern for surgeons. This is because it is associated with other surgical and medical complications such as bleeding, postoperative ventilation > 48 hours, and pneumonia.[25] Free flap surgery should still be performed by considering the safety and effectiveness for the patient due to the current increase in skill and experience in microsurgery.

Hypertension

As with DM, hypertension has long been considered a risk for patients and flaps in microsurgery. Histopathologically, the intima is thickened with calcifications and fibrofatty plaques. The presence of atheroma in these small arteries will make surgery more difficult. Surgeons' expertise and experience are crucial to success.[31] Early studies of the effect of hypertension on the arterial anastomosis of rats also demonstrated a similar response to platelets and other blood products in suturing lines than in controls.[32] The hypertension factor in other studies did not show any difference between the successful free flap group and the complication group. [33, 34, 35] In our meta-analysis of five articles, the results were consistent where comorbid hypertension was not significant as a risk factor for flap failure. Several other study findings show contradictory results. Chung et al. said the association of hypertension with surgical complications such as surgical site infection (ILO) was significant.[36] Another journal on breast reconstruction with free tissue transfer, revealed hypertension as one of the readmission risks in 0-90 days after surgery due to surgical complications.[37] Most of the comorbidities of hypertension are related to surgical complications, although it is not clear that it directly causes failure.

Operation duration

The duration of the operation includes procedures such as ablation, neck dissection, donor harvesting and other procedures performed during reconstruction.[38] The duration of the operation is often considered representative of the operating technique or skill of the operator. Surgeon experience is one of the critical success factors for microsurgical anastomosis.[39] Long operation duration was associated with ischemic time. At this time there are structural changes, endothelial metabolism, production of inflammatory mediators that encourage tissue damage. Longer duration of general anesthesia (>18 hours) is associated with free flap failure due to higher complexity and greater fluid administration.[40] There will be more complications from surgery, especially medical complications.[41] Duration of surgery more than 640 minutes (10.3 hours) in this study was not significant for free flap failure. These results differ from many theories from the previous literature. Another result of breast reconstruction with bilateral free flaps did not find a significant relationship with failure compared to unilateral free flaps even though the operating time was longer.[42] Surgical time has not been reported to be associated with an increase in overall complications (early or late) in free flap breast reconstruction.[43] Gürlek et al. wrote that flap loss was not found to be significantly different between groups with ischemic time less than and more than 3 hours in head neck and breast reconstruction in Texas.[44] It can also be explained that this difference is caused by other confounding factors that obscure the results such as flap size and dimensions, vascular size.[45] However, more studies are needed to be included in the meta-analysis. Longitudinal operation does not mean that the operator performs the operation slowly, but is secondary to the difficult situations encountered, such as the complexity of flap harvesting, inset, or anastomosis. Multiple procedures involving other surgeons such as tumor ablation, debridement, or bone reconstruction have contributed to the length of surgery.[34]

Blood transfusion

Blood transfusions are often given in microsurgery which takes a long time due to slow but continuous blood loss. Erythrocytes in the blood bag have changed so that hemolysis easily occurs. The release of hemoglobin will reduce the concentration of nitric oxide resulting in vasoconstriction, leukocyte adhesion, macrophage activation. The combination of these events will increase the risk of thrombosis, coupled with an increase in blood viscosity. Karamanos et al. [46] revealed a higher incidence of reoperation due to flap complications in patients receiving transfusion (42 vs. 10%, $p < 0.001$). While a study revealed that the number of packed red cell (PRC) units administered during surgery was not associated with postoperative complications.[47] Analysis by Kim et al showed that blood transfusion was not a predictor of flap failure.[48] On the other hand, intraoperative blood transfusion is a significant risk factor for overall complications and medical complications.[49] The role of blood transfusion in flap loss cannot be concluded from this meta-analysis because none of the articles met the criteria. However, a restrictive strategy is recommended: blood transfusion at hemoglobin less than 7 g/dl.[3]. The decision to give or restrict blood transfusion depends on the surgeon and anesthetist according to the patient's overall condition and hemodynamic status of the patient.

Intraoperative fluid administration

The flap is prone to fluid overload due to the absence of lymphatic drainage and ischemia, especially when the vasculature is clamped. The anesthesiologist will control hemodynamics with fluid so that circulating volume and oxygenation to the flap are maintained. Inadequate fluid will cause hypovolemia and hypoperfusion, which will trigger ischemic-reperfusion injury and inflammation resulting in flap failure. Fluid therapy in a certain amount that causes hemodilution will interfere with oxygenation due to lack of erythrocytes. Meanwhile, another opinion states that hemodilution will increase oxygenation as microcirculation increases. Therefore, there is still a debate between giving fluids without restriction or with restrictions. However, various reviews and clinical trials support the restriction of fluid therapy. A study by Booi [50] found that patients who returned to the operating room due to thrombus formation at the anastomotic site had a history of being given more fluid therapy. Administration of large volumes of fluid (>7 ml/kg/hour) was found to be associated with postoperative flap complications such as partial loss, dehiscence, infection and fat necrosis. Meanwhile, giving more restricted fluids will result in better tissue perfusion and shorter duration of stay.[46] In another study, there was one flap failure in the liberal fluid administration (LFA) cohort, while no major complications were found in the fluid-

restrictive vasopressor-dominated (FRV) cohort.[51] The average volume of crystalloid administration in the group with flap failure was higher than that without failure (5,634 ml vs 5,420 ml).[52]
The increase in intravascular volume of crystalloid fluid can increase inflammation and clotting rate as well as excess edema in the flap and recipient area.[40]. This event will mechanically compress the pedicle. Fluid overload will cause venous stasis and impair arterial perfusion in retrograde. Administration of crystalloid fluids of more than 7 L during surgery is also associated with major medical complications (cardiovascular, respiratory, and central nervous system).[53] Based on these findings, it is recommended to limit intravenous fluid therapy or be given in a guided manner through central venous pressure (CVP) or arterial monitoring. Goal-directed haemodynamic therapy (GDHT) was used to dynamically evaluate intraoperative fluid adequacy based on parameters of stroke volume variation, mean arterial pressure, cardiac index. GDHT has been shown to reduce intraoperative fluid use and length of stay.[54] However, in this study a meta-analysis could not be carried out due to limited data in the analyzed studies. In addition, it was also found that the effect sizes and categories used in the various studies were not similar.

## 5. Conclusion

Old age is not significant as a risk factor for free flap failure, but overall it has a risk for postoperative medical complications. There was no difference between men and women as a risk factor for free flap failure. Diabetes mellitus and hypertension comorbidities were not significant risk factors for free flap failure, but were associated with other medical and surgical complications. Longer operation duration was not significantly associated as a risk factor for free flap failure. The factor of blood transfusion and intraoperative fluid administration has not been proven to have an effect on total flap necrosis in this study.

**Acknowledgment.**
None.

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