

## Peer Review File

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### Review Comments

#### Reviewer A

Thank you for the time you dedicated to revise our manuscript. Here some replies to your comments.

Comment 1: “There are several edición mistakes . Pag 4 71 Ackground/ background”

**Reply:** corrected with “Background”.

Comment 2: “74/75 non gaps between words.please review à”

**Reply:** done

Comment 3: “Pag 5121 head and neck district.”

**Reply:** done. Modified according to Reviewer C’s suggestion.

Comment 4: “Pag 10, 268 ample, please review”

**Reply:** done. Modified according to Reviewer C’s suggestion.

Comment 5: “They have to define many concepts. Pag 6, 131-132. The first thing to define is the algorithm for working with Flotraq. There is a maintenance fluid, ?they administered an extra bolus.colloids when VS is low,? they work only with bolus?.

How is fluid mbntenice in PACU, a liberal fluid therapy, GDT?. The first 24h after surgery are determinat in free flap viability”

**Reply: defined. Specified as follows:** “ FloTrac™ system is based on an algorithm that allows to extrapolate hemodynamic parameters such as cardiac output (CO), cardiac index (CI), stroke volume (SV), stroke volume index (SVI) and stroke volume variation (SVV) from the arterial pressure waveform. All patients received intraoperative fluid maintenance therapy at the discretion of the anesthesiologist. For patients receiving invasive hemodynamic monitoring, additional fluid challenge was performed according to SVV value and inotropes and vasopressor were started to maintain adequate CI and mean arterial blood pressure.” Postoperative fluidic therapy was, unfortunately, not guided by GDT so it was not considered in patient’s fluidic balance nor as a variable in the present study.

Comment 6: “Pag 7 line 174: Most of the patients... please define, the results are completely different in non oncological and oncological patients . It must be an important study bias.”

**Reply:** defined. Modified as follows: “Out of all patients, 72.1% underwent surgery for malignant tumor resection. The remaining 27.9% were diagnosed with non-malignant conditions, including keratocysts or other benign cysts (8.6%), ameloblastomas (5.8%), osteonecrosis and osteomyelitis (3.4%). Additionally, some patients required secondary reconstruction after cancer resection (8.2%) or due to trauma (1.9%).” In this study, the oncological condition was not found to be a predictor of postoperative complications, as evidenced in Table 3.

Comment 7: “Pag 7. 181. How long the complications have been recorder? One day, one week, one

month after surgery? Mortality is ver high for a short period.”

**Reply:** Complications were recorded during the hospital stay that was on average of 25 days. Three patients died over a 17-year period.

Comment 8: “Pag 8, 193/203 It is necessary to read at least twice for understand that they are talking about to different hypertension Please clarify”

**Reply:** Modified as follows. “As reported in Table 3, the multivariate model developed for the analysis of postoperative complications showed that a history of arterial hypertension (OR: 0.27, 95% CI: 0.08-0.95, P:0.04) and higher intraoperative hemoglobin values at the end of surgery (OR: 0.46, 95% CI: 0.25-0.83, P:0.01) were associated with a reduced risk of major surgical complications. In this study, a history of alcohol abuse and postoperative RBC transfusions appear to be linked with a higher risk of major surgical complications, although this correlation does not reach statistical significance. Strong predictors of postoperative medical complications were: length of postoperative ICU stay (OR:1.62, 95% CI:1.30-2.03, P: 0.008), tumor stage T1-2 (OR:3.00, 95% CI:1.28-6.90, P:0.03), tumor stage T3-4 (OR:4.40, 95% CI:3.73-12.31, P: 0.006) and a history of arterial hypertension (OR:3.73, 95% CI:1.20-11.55, P: 0.02).”

Initially, it is mentioned that a history of arterial hypertension reduces the risk of major **surgical** complications, later it is stated that this history of hypertension is a strong predictor of **medical** complications.

Comment 9: “Pag 8, 207 Review . It s seems a hight fluid rate for goal directed therapy and head and neck recommendations about fluid therapy. Also there is a high transfusion rate.”

**Reply:** The study retrospectively includes patients that underwent surgery over the last 18 years. Despite evidence suggesting near zero balance or GDT fluidic therapy being previous to our first cases, ERAS recommendations on free flap reconstruction for H&N were first published in 2017. Previous fluidic and RBC transfusion management tended to be more “liberal”.

Comment 10: “Pag 9, 224. The results would be different depending on the oncological and non oncological patients percentage. The Flotraq use its not there difference in results, the way of working on it I can be decisive on the results. There is an important bias factor Have been the same anesthesia team working with and with out GDT?”

**Reply:** In this study, the oncological condition was not found to be a predictor of postoperative complications, as evidenced in Table 3. The anesthesia team involved in head and neck surgery remained unchanged during the study period, except for turnover due to retirements and/ or the hiring of new personnel.

### **Reviewer B**

“Thank you for the opportunity to review the manuscript, "Goal-directed Therapy in Free Flap Reconstructive Surgery." This paper presents insights into the management and outcomes of free flap reconstructive surgery in the head and neck region. The authors conducted a retrospective cohort study to investigate various factors associated with medical and surgical complications in these patients and assessed the impact of invasive hemodynamic monitoring. The paper is generally well-structured and contains some novel findings. The use of the Strengthening the Reporting of

Observational Studies in Epidemiology (STROBE) reporting checklist is appropriate. However, there are some specific areas that need to be addressed for the paper to be suitable for publication.”

Thank you for your time spent reviewing our manuscript. Below are our responses to your comments. Your comments and suggestions are precious for enhancing the quality of our work”

Comment 1: “1. Key points: The authors should avoid statements that imply causality given the retrospective design of the study. For example the authors should not state that any of the interventions reduced complications as only associations can be established from these data.”

**Reply:** Revised as follows. “In this study the use of invasive hemodynamic monitoring is associated with a reduction in intraoperative fluid administration, but consequent role of vasopressors is discussed.

The use of invasive hemodynamic monitoring is associated with an increased administration of vasopressors without a corresponding rise in complication rates. Additionally, it appears to decrease the length of hospital stays.”

Comment 2: “2. The abstract provides a concise overview of the study but could benefit from more detailed results specifying medical and surgical complications, as well as the impact of invasive hemodynamic monitoring.”

**Reply:** Modified as follows: “Higher intraoperative hemoglobin values at the end of surgery (OR: 0.46, 95% CI: 0.25-0.83, P:0.01) and arterial hypertension (OR: 0.27, 95% CI: 0.08-0.95, P:0.04) were associated with a reduced risk of postoperative surgical complications. “.

The impact of invasive hemodynamic monitoring is reported here “The use of invasive hemodynamic monitoring is associated with a reduction in intraoperative fluid administration (8.2 vs 9.5 ml/kg/h, P: 0.008), increased use of vasopressors (OR=2.53, P=0.003) and reduction of the length of hospital stay (20 vs 23 days, P: 0.04)”.

Comment 3: “3. The introduction provides a clear rationale for the study. However, the background is not complete. The authors mention the work of the Society of Head and Neck Anesthesia (SHANA) but do not cite one of the most relevant recent paper. Please cite the following paper: “Expert Consensus Statement on the Perioperative Management of Adult Patients Undergoing Head and Neck Surgery and Free Tissue Reconstruction From the Society for Head and Neck Anesthesia. Healy DW, et al. Anesth Analg. 2021 Jul 1;133(1):274-283. doi: 10.1213/ANE.0000000000005564.PMID: 3412759”.

**Reply:** Done, reference n\*6.

Comment 4: “4. In the methods section, it would be useful to describe how patients were selected for inclusion and whether any exclusion criteria were applied in more detail. Also, the study period ranges from 2005 to 2022, making it important to address any changes in surgical techniques, perioperative care, or guidelines that may have occurred during this time.”

**Reply:** We incorporated specific exclusion criteria. Given the extensive 17-year timeframe we examined, we acknowledge the substantial changes that occurred in perioperative and anesthesiological care. Our analysis focused on assessing the impact of key management factors that evolved during this period, such as the volume of administered fluids, the utilization of

hydroxyethyl starch, albumin, and vasopressors, as well as the adoption of invasive hemodynamic monitoring. Additionally, we emphasized this aspect as a limitation of the study in Section 4.2 – Strengths and Limitations. (“Finally, it is difficult to rule out the possible impact of confounding factors, such as the surgeons learning curve, the modifications in the surgical technique and in the perioperative anesthesiological management.”).

Comment 5: “5. As to results, the relationship between the use of invasive hemodynamic monitoring and postoperative complications is discussed but not presented in a table or figure. This might be considered for clarity. Also, the authors might consider discussing the potential implications of transfusion versus crystalloid in terms of volume, edema, and perfusion.”

Reply: Thank you for the comment. We did not present a table showing the relationship between invasive hemodynamic monitoring and postoperative complications because no statistically significant relationship was found. It would be very interesting to further evaluate the potential role of RBC transfusions or volume of crystalloids on intra- and extravascular liquid volume and on perfusion but unfortunately our dataset would be insufficient for that purpose.

Comment 6: “6. In the discussion, please consider how the retrospective and single-center nature of the study may limit generalizability. This study did not find an association between fluid volume and risk of complications, but other literature has suggested such association; care must be taken in generalizing such data. The finding that arterial hypertension was associated with reduced risk of major surgical complications is a novel result but also requires further study in more rigorous designs.”

**Reply:** In Section 4.2 we highlighted the study limitations. Furthermore we emphasized the need for further investigation regarding the role of hypertension in postoperative complications (refer to the text in red in Section 4.2) and exploring the impact of fluid volume (text in red in Section 4.4).

Comment 7: “The conclusions should be tempered to state that the findings support a role for goal-directed therapy and for standardized guidelines, rather than stating that the findings definitively establish these approaches to be superior (as there still is some controversy)”.

**Reply:** revised. See text in red in Conclusion.

Comment 8: “8. Language and Clarity: The language and clarity of the paper are generally good, but there are instances of phrasing that could be improved for clarity. A few examples are listed below, but a native English speaker review would be ideal:

-in the Abstract, "a secondary was to investigate" should be corrected to "a secondary objective was to investigate."

-In the introduction, surgery to remove tumor should be described as “ablative” or “extirpative” not “demolitive”

-“Regarding amine and colloids, our finding is consistent with analogous results

282 been reported by other authors (11, 19, 22-24),” should state “results that have been reported...”

-“A standardize precise protocol regarding the use of goal directed therapy

294 should be validated on larger cohorts of patients to improve outcomes” should be changed to “standardized”

-“do not appear to have a significant clinical impact" could be more clearly stated as "do not appear

to significantly impact clinical outcomes.””

**Reply:** We have thoroughly revised the manuscript with the assistance of a native speaker, aiming to enhance its clarity and readability. We hope that the text is now significantly clearer and easier to read.

Comment 9: “In summary, this article provides valuable insights into the factors influencing complications in free flap reconstructive surgery and supports the importance of goal-directed therapy. With some minor revisions, it has the potential to make a meaningful contribution to the field.”

**Reply:** Once more, thank you for granting us the opportunity to publish in JOMA and for the effort you dedicated to our work.

### **Reviewer C**

Thank you for taking the time to peer review our manuscript. Please find our responses to your comments below

Comment 1: “In the attached pdf file I have made point-by-point corrections to the article. It is important to make corrections to the English used in the paper before publication.”

**Reply:** The document has been revised as you suggested, and modifications are indicated using red text for easy identification. Thank you for the time you dedicated to revise our manuscript and for your comments.

Comment 2: “It is necessary to remind the authors that since this is a retrospective study, no statements about causality can be made; this must be corrected in the article.”

**Reply:** The document has been revised with a specific focus on this aspect, modifications are indicated using red text for easy identification.

Comment 3:”The paper states that it is the first article that finds high blood pressure as a protective factor in free flap reconstruction. This is not the case and there are several previous articles that expose this. An example article could be the following:

Otolaryngol Head Neck Surg

. 2019 Oct;161(4):598-604. doi: 10.1177/0194599819860809. Epub 2019 Aug 6.

Factors Associated with Free Flap Failures in Head and Neck Reconstruction

Meghan B Crawley 1, Larissa Sweeny 1, Prasanti Ravipati 2, Ryan Heffelfinger 1, Howard Krein 1, Adam Luginbuhl 1, Richard Goldman 1, Joseph Curry 1

Affiliations expand

PMID: 31382816 DOI: 10.1177/0194599819860809

Abstract

Objective: To investigate causes of failure of free flap reconstructions in patients undergoing reconstruction of head and neck defects.

Study design: Case series with chart review.

Setting: Single tertiary care center.

Subjects and methods: Patients underwent reconstruction between January 2007 and June 2017 (n = 892). Variables included were clinical characteristics, social history, defect site, donor tissue, ischemia time, and postoperative complications. Statistical methods used include univariable and multivariable analysis of failure.

Results: The overall failure rate was 4.8% (n = 43). Intraoperative ischemia time was associated with free flap failures (odds ratio [OR], 1.062; 95% confidence interval [CI], 1.019-1.107; P = .004) for each addition of 5 minutes. Free flaps that required pedicle revision at time of initial surgery were 9 times more likely to fail (OR, 9.953; 95% CI, 3.242-27.732; P < .001). Patients who experienced alcohol withdrawal after free flap placement were 3.7 times more likely to experience flap failure (OR, 3.690; 95% CI, 1.141-10.330; P = .031). Ischemia time remained an independent significant risk factor for failure in nonosteocutaneous free flaps (OR, 1.105; 95% CI, 1.031-1.185). Alcohol withdrawal was associated with free flap failure in osteocutaneous reconstructions (OR, 5.046; 95% CI 1.103-19.805) while hypertension was found to be protective (OR, 0.056; 95% CI, 0.000-0.445). Conclusion: Prolonged ischemia time, pedicle revision, and alcohol withdrawal were associated with higher rates of flap failure. Employing strategies to minimize ischemic time may have potential to decrease failure rates. Flaps that require pedicle revision and patients with a history of significant alcohol use require closer monitoring.

Keywords: free flap; head and neck reconstruction; surgical complications.”

Reply: Thank you for the correction. We included the cited article in our bibliography and corrected the text as follows: “ It emerged that a history of arterial hypertension and the presence of higher hemoglobin values at the end of surgery seem to reduce the risk of major postoperative surgical complications. A potentially protective role of arterial hypertension on flap failure rate has been previously described by Crawley et al. (27); this association, however, is partly offset by the potentially harmful role of an history of arterial hypertension on postoperative medical complications and warrants additional investigation, especially considering the retrospective and single-center design of the study.

Comment 4: “The rest of the modifications to be made are explained in the pdf.

Additional comments of reviewer C:

L71: Background

L75: demolitive, guaranteeing: change the term for another, e.g. Oncologic surgery

L80: should use more concise language

L106: possibly influencing: that may affect

L107: after-in

L112: ~~introduction of a~~

L120: All patients over 18 years of age reconstructed with free flaps in the head and neck region were included.

L189: Patients. Pneumonia was the most common infectious complication.

L201: If all tumor stages (T1, T2, T3, T4) increase the risk of in-hospital complications, it should be expressed that way, not differentiating T1-T2 from T3-T4. It should be expressed as: patients with microsurgical reconstructions with oncological etiology had a greater number of complications than non-oncological patients. The risk of complications was greater with higher tumor stage.

L213: ~~the pre-established~~

L217: It is important to remember that retrospective studies do not allow us to study the temporal relationship between cause and effect and, therefore, they rarely serve to indicate causality.

L233: Prolonged stay in the ICU seems to be an obvious risk factor for postsurgical complications.

L234: What comorbidity indices are you referring to?

L247: change district, e.g. head and neck region

L250: This paper Facial Plastic and Reconstructive Surgery Factors Associated with Free Flap Failures in Head and Neck Reconstruction Meghan B. Crawley MD, Larissa Sweeny MD, Prasanti Ravipati, Ryan Heffelfinger MD, Howard Krein MD, Adam Luginbuhl MD, Richard Goldman MD, Joseph Curry MD First published: 06 August 2019 <https://aao-hnsfjournals.onlinelibrary.wiley.com/doi/10.1177/0194599819860809> demonstrate the protective role of arterial hypertension on flap failure rate. while hypertension was found to be protective (OR, 0.056; 95% CI, 0.000-0.445).

L259: The incidence of flap failure is not low in the study series. This is a higher failure rate than publications from other microsurgical groups (1-5%). What is low is the n of the sample under study.

L268: Change to:

Different studies have evaluated the impact of comorbidities on the outcome of patients undergoing free flap transfer, identifying several risk predictors such as age, comorbidity indices, smoking, intraoperative hemoglobin values, and perioperative fluid management. (7-9)

L282: There is a progressive consensus based on greater scientific evidence on the use of vasopressors in reconstructive microsurgery.

Vasopressors improve outcomes in autologous free tissue transfer: A systematic review and meta-analysis.

Noori O, Pereira JL, Stamou D, Ch'ng S, Varey AH.

J Plast Reconstr Aesthet Surg. 2023 Jun;81:151-163. doi: 10.1016/j.bjps.2022.08.069. Epub 2022 Aug 27.

PMID: 36379854 Review.

**Reply:** Revised according to reviewer C's suggestions. We observed that you emphasized the hypertension data in tables 1 and 3. Upon thorough review, we have confirmed the accuracy of the information. However, we would appreciate your clarification on the specific aspects you intended to emphasize or draw attention to. We revised bibliography as you suggested.