Rihards Pēteris Ročāns

ORCID 0000-0002-3546-5612

Biomarkers for Predicting Complications in Microvascular Flap Surgery

Summary of the Doctoral Thesis for obtaining the scientific degree "Doctor of Science (*PhD*)"

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Supervisors of the Doctoral Thesis:

Dr. med., Professor Emeritus **Biruta Mamaja**,
Rīga Stradiņš University, Latvia

Dr. med., Associate Professor **Simona Doniņa**,
Rīga Stradiņš University, Latvia

Official Reviewers:

Dr. med., **Mārtiņš Kapickis**,
Latvian Microsurgery centre

Dr. med., Associate Professor **Iveta Golubovska**,
University of Latvia

Dr. med., Professor **Diana Bilskiene**,
Lithuanian University of Health Sciences

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The Doctoral Thesis is available in RSU Library and on RSU website:
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Secretary of the Promotion Council:

Dr. med., Associate Professor **Ģirts Šalms**

Table of Contents

Abbreviations used in the Thesis

CONUT	Controlling Nutritional Status Score
vWF	von Willebrand factor
vWF:Ag	von Willebrand factor antigen
TGF-β	Transforming growth factor beta
TGF-β1	Transforming growth factor beta-1

Introduction

Microvascular flap surgery has become a common method in reconstructive surgery for addressing a wide range of tissue defects (Lese et al., 2021). These defects may arise from causes such as trauma, cancer, chronic infections, or complex wounds of multiple etiologies (Min et al., 2022). Compared to conventional surgical techniques, free flaps offer improved quality of defect correction, greater donor site flexibility, faster recovery, shorter hospital stays, and reduced treatment costs (Galviz Tabarez et al., 2025).

Despite advancements in surgical methods and decreasing rates of complications, flap loss remains a challenge (Lo et al., 2017). Complications are generally classified into three categories: true flap loss, minor flap complications, and flap hematoma (Lo et al., 2017; Vincent et al., 2019; Min et al., 2022). Throughout previous research, the overall complication rate ranges from 3% to 6% (Hanasono et al., 2008; Dolan et al., 2012; Lese et al., 2021). Venous thrombosis is identified as the most common cause of true flap loss, while arterial thrombosis tends to be the primary contributor to early flap loss (Stevens et al., 2023). In venous flap thrombosis, pedicle kinking is a more prevalent cause of flap failure than anastomotic failure (Williams et al., 2004). Despite the technical complexity of microvascular flap transplantation, systemic responses to surgical trauma, including immune activation and coagulation processes, play a significant role in predicting the outcomes (Schuderer et al., 2023). Recent studies have highlighted the biological mechanisms underlying flap-related complications and have proposed the use of specific biomarkers for risk stratification before surgery (Chargi et al., 2022). These biomarkers may offer significant opportunities to evaluate the risk of true flap loss, improve our understanding of flap complication pathophysiology and refine perioperative care protocols.

Numerous studies have shown that malnutrition significantly contributes to complications across various surgical populations (Reed et al., 2024; Portuondo et al., 2020; Tobert et al., 2017). Malnourished patients are more prone to postoperative issues such as wound dehiscence, infection, and fistula formation, often requiring reoperation and increasing morbidity and hospital costs (Le et al., 2023; Quian et al., 2021). As nutritional status is a modifiable risk factor, early screening, assessment, and intervention can help reduce postoperative complications (Venianaki et al., 2021; Yu et al., 2020). Laboratory biomarkers, routinely included in preoperative assessments, offer a convenient means of malnutrition risk screening (Yu et al., 2020; Takagi et al., 2019). Given the complexity of microvascular flap reconstruction and the availability of effective nutritional intervention strategies, using biomarkers of malnutrition could improve surgical outcomes (Jaxa-Kwiatkowski et al., 2025; Yu et al., 2020). Common laboratory markers for malnutrition risk include serum albumin,

prealbumin, transferrin, and total lymphocyte count (Keller, 2019). The Controlling Nutritional Status (CONUT) score, a simple tool based on serum albumin, total cholesterol, and lymphocyte count, has proven effective in predicting postoperative outcomes across multiple surgical populations (Lo Buglio et a., 2024; Ulibarri et al., 2005). Due to its versatility, simplicity, and predictive value, the CONUT score may represent a promising tool for evaluating nutritional risk in microvascular flap surgery patients.

In addition to malnutrition, systemic inflammation plays a role in flap thrombosis and minor flap complications (Chargi et al., 2022). Low blood albumin levels are linked to elevated proinflammatory mediators and impaired tissue regeneration, while high fibrinogen levels are associated with inflammation and tissue repair, often serving as a predictor of complications (Eckart et al., 2020; Luyendyk et al., 2019). While individual biomarkers can predict surgical outcomes, recent studies show that combined measures enhance predictive accuracy and improve prognostic value (Ren et al., 2024; Zhang et al., 2021; Tomita et al., 2020). The fibrinogen-to-albumin ratio (FAR) is a promising combined measure that has demonstrated strong potential for assessing postoperative outcomes across various surgical populations (Altin et al., 2025; Park et al., 2022).

The detailed pathophysiology of true flap loss, although involving chronic inflammation, is currently not fully defined (Chargi et al., 2022). True flap loss has been associated with elevated fibrinogen, von Willebrand factor (vWF) function, and vWF antigen (vWF:Ag) (Rothweiler et al., 2021; Drizlionoka et al., 2019, Du et al., 2015; Handschel et al., 2013). Elevated vWF:Ag levels, often resulting from endothelial damage or inflammation, can promote platelet aggregation and adhesion, exacerbating thrombotic risks in reconstructive surgery (Rothweiler et al., 2021). The interaction between vWF and inflammatory biomarkers in the context of thrombotic events remains complex, though studies by Handschel et al. and Rothweiler et al. demonstrate the significant role of vWF:Ag in true flap loss (Rothweiler et al., 2021; Handschel et al., 2013). However, the full extent of vWF:Ag interactions with other risk factors, including chronic inflammation, remains elucidated.

It is generally accepted that microvascular flap surgery provokes a predominantly proinflammatory immunologic response (Schmidt et al., 2007, Zhang et al., 2006). Elevated levels of proinflammatory cytokines, including interleukin-6, interleukin-8, and macrophage colony-stimulating factor, have been associated with ischemia-reperfusion injury in microvascular surgery (Finke et al., 2018). Nevertheless, there is a lack of studies specifically addressing the contribution of immunomodulatory cytokines to the pathophysiological mechanisms underlying microvascular flap complications. Although previous investigations have assessed cytokine levels within flap venous blood samples (Finke et al., 2018), no studies

evaluate the postoperative change in immunomodulatory cytokine concentrations in regular circulating blood samples. Transforming growth factor beta (TGF-β), a pleiotropic cytokine, is involved in multiple cellular processes, including immunoregulation, inflammatory resolution, and tissue repair (Deng et al., 2024). The principal isoform, transforming growth factor beta 1 (TGF-β1), has emerged as a potential biomarker, influencing thrombogenesis and thrombus stabilization (Zhang et al., 2024). TGF-β1 is predominantly released from platelet alpha-granules and becomes bioactive under conditions of shear stress, which could have pathophysiological and predictive implications in true flap loss (Ahamed et al., 2008).

Despite growing interest in the use of biomarkers for risk stratification in microvascular flap surgery, there remains a lack of validated, clinically applicable models that integrate nutritional, inflammatory, and thrombosis-related markers with patient outcomes (Chargi et al., 2022; Vanags et al., 2020; Yu et al. 2020). This research aims to address this gap by investigating the prognostic value of combined biomarkers, including the CONUT score, FAR, as well as emerging individual biomarkers such as TGF-β1 and vWF:Ag, to enhance preoperative risk assessment and perioperative care in microvascular flap surgery.

Aim of the Thesis

The aim of this study is to establish novel biomarker models for the preoperative and early postoperative prediction of microvascular flap complications in reconstructive surgery.

Objectives of the Thesis

The following objectives are set to reach the aim of the Doctoral Thesis:

1. Outline novel avenues for best practice and provide an outlook for further research on preoperative risk assessment, anesthesia, and perioperative care in microvascular flap surgery.
2. Assess the predictive value of the CONUT score for predicting complications in elective microvascular flap surgery.
3. Evaluate the predictive value of FAR in predicting various complication types in elective microvascular flap surgery.
4. Determine the predictive value of vWF:Ag for microvascular flap complications and investigate the relationship between markers of chronic inflammation and increased vWF:Ag in various complication types.
5. Assess the prognostic significance of postoperative TGF-β1 changes in relation to various microvascular flap complications and to examine the link between perioperative TGF-β1 levels and other biomarkers in microvascular flap surgery patients.

Hypotheses of the Thesis

- Increased preoperative CONUT score effectively predicts malnutrition and postoperative complication risk for microvascular flap surgery patients.
- Increased preoperative FAR predicts the risk of true flap loss in microvascular flap surgery.
- Increased preoperative plasma vWF:Ag is linked to a proinflammatory state and is predictive for complications in microvascular flap surgery.
- A significant postoperative increase in serum TGF-β1 relative to its preoperative level demonstrates early predictive value and is associated with true flap loss.

Conclusions

1. Perioperative care strategies for anaemia correction, analgesia, and PNB use are well-supported by current evidence in microvascular flap surgery. However, other aspects such as malnutrition assessment, inflammation, hypercoagulability, fluid and temperature management, and antithrombotic treatment strategies remain less clearly defined. The use of biomarkers to predict true flap loss represents a promising direction for future research.
2. Preoperative CONUT score > 2 is a reliable marker of malnutrition risk and predictor of minor flap complications. Patients with lymphocytopenia, monocytopenia, low haematocrit, or obesity, are at increased risk of minor flap complications, highlighting the need for routine malnutrition risk screening and targeted interventions in microvascular flap surgery.
3. Preoperative FAR shows a U-shaped association with flap complications, where low FAR below 0.06 predicts flap hematoma or true flap loss, high FAR above 0.10 predicts minor flap complications, and both are linked to longer hospital stays, supporting its utility as a preoperative risk stratification tool in microvascular flap surgery.
4. Elevated preoperative vWF:Ag levels above the cut-off of 163.73 IU/dL are linked to increased risk of true flap loss. Preoperative vWF:Ag concentration is positively associated with inflammatory biomarkers including increased fibrinogen, neutrophil-lymphocyte ratio, interleukin-6, c-reactive protein, and decreased plasma albumin, supporting the role of vWF:Ag as a predictive marker for true flap loss.
5. Postoperative increase in TGF-β1 greater than 1.00 ng/mL, driven by both shear stress induced platelet activation at sites of anastomotic dysfunction and active thrombus formation, is an effective biomarker for early detection of impending true flap loss.
6. Novel biomarker models integrating nutritional, inflammatory, coagulation, and immunological markers are useful for predicting complications in microvascular flap surgery. The newly identified perioperative biomarkers can help identify high-risk patients, guide perioperative care, and enable early detection of impending true flap loss. These insights support a more personalized, data-driven approach to improving outcomes in microvascular flap surgery

Proposals

1. Patients with a preoperative CONUT score > 2 are at a higher risk of flap complications and may benefit from nutrition interventions.
2. Preoperative FAR evaluation is recommended, as patients with both a high and a low preoperative FAR are at a higher risk of flap complications.
3. Preoperative vWF:Ag levels can be used to identify patients with a higher risk of true flap loss.
4. Monitoring preoperative TGF-β1 biomarker can be used for early detection of flap compromise and may help guide the decision to perform early anastomosis revision.
5. Further multicentre research is needed to validate our biomarker models integrating nutritional, inflammatory, coagulation, and immunological markers to support the development of personalized perioperative care in microvascular flap surgery.

List of publications, reports and patents on the topic of the Thesis

Publications:

1. Rocans, R. P., Zarins, J., Bine, E., Deksnis, R., Citovica, M., Donina, S., Mamaja, B. (2023). The Controlling Nutritional Status (CONUT) Score for Prediction of Microvascular Flap Complications in Reconstructive Surgery. *Journal of Clinical Medicine*, 12(14), 4794. https://doi.org/10.3390/jcm12144794
2. Rocans, R. P., Zarins, J., Bine, E., Mahauri, I., Deksnis, R., Citovica, M., Donina, S., Vanags, I., Gravelsina, S., Vilmane, A., Rasa-Dzelzkaleja, S., Mamaja, B. (2024). Von Willebrand Factor Antigen, Biomarkers of Inflammation, and Microvascular Flap Thrombosis in Reconstructive Surgery. *Journal of clinical medicine*, 13(18), 5411. https://doi.org/10.3390/jcm13185411
3. Ojuva, A. M., Rocans, R. P., Zarins, J., Bine, E., Mahauri, I., Donina, S., Mamaja, B., Vanags, I. (2024). Novel Challenges and Opportunities for Anesthesia and Perioperative Care in Microvascular Flap Surgery: A Narrative Review. *Clinics and Practice*, 14(5), 2187-2201. https://doi.org/10.3390/clinpract14050172
4. Rocans, R. P., Zarins, J., Bine, E., Mahauri, I., Deksnis, R., Citovica, M., Donina, S., Vanags, I., & Mamaja, B. (2025). Fibrinogen-to-albumin ratio (FAR) for predicting microvascular flap complications in reconstructive surgery. *JPRAS open*, 44, 414–423. https://doi.org/10.1016/j.jpra.2025.03.022.
5. Rocans, R. P., Zarins, J., Bine, E., Mahauri, I., Deksnis, R., Citovica, M., Donina, S., Gravelsina, S., Vilmane, A., Rasa-Dzelzkaleja, S., Sabelnikovs, O., Mamaja, B. (2025). Early Postoperative Increase in Transforming Growth Factor Beta-1 Predicts Microvascular Flap Loss in Reconstructive Surgery: A Prospective Cohort Study. *Medicina (Kaunas, Lithuania)*, 61(5), 863. https://doi.org/10.3390/medicina61050863

Reports and theses at international congresses and conferences:

1. Rocans R.P., Mamaja B, Doniņa S43 *General or regional anaesthesia for microvascular flap surgery: comparison of surgical complication rate and duration of hospitalization.* Regional Anesthesia & Pain Medicine 2021;70:A25. European Society of Regional Anaesthesia Hybrid Conference, 2021 (Poster presentation)
2. Rocans R. P., Mamaja B, Doniņa (2022) *General or regional anaesthesia for microvascular flap surgery: comparison of surgical site infection rate.* Abstract from Euroanaesthesia 2022, AS-ESAIC-2022-00339. European Society of Anaesthesia and Intensive care, Milan, Italy, 2022 (Oral presentation)
3. Rocans, R. P., Zarins, J., M., Donina, S., Mamaja, B. *Full Blood Count Biomarkers for Prediction of Flap Complications in Microvascular Flap Surgery.* RSU International Research Conference 2023: Knowledge for Use in Practice. Riga Stradiņš University, Riga, Latvia, 2023 (Poster presentation)
4. Rocans R. P., Zarins, J., Mamaja B, Doniņa (2023) *Biomarkers for the preoperative prediction of flap loss in microvascular flap surgery: a single-center prospective analysis.* Abstract from Euroanaesthesia 2023, AS-ESAIC-2022-00339. European Society of Anaesthesia and Intensive care, Glasgow, Scotland, UK, 2023 (Oral presentation)
5. Rocans R. P., Zarins J, Deksnis R, Citovica M, Bine M, Mamaja B, Doniņa S. (2024) *The Use of Peripheral Nerve Blocks for Extremity Microvascular Flap Surgery: Comparison of Different Surgical Complications.* Baltic Society of Regional Anaesthesia 9th International Conference of Baltic Society of Regional Anaesthesia, Kuresaare, Estonia, 2024 (Oral presentation)

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