



CLINICAL OUTCOMES, REJECTION PATTERNS, AND IMMUNOSUPPRESSIVE STRATEGIES IN VASCULARIZED COMPOSITE ALLOTRANSPLANTATION: A PRISMA-BASED SYSTEMATIC REVIEW

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ABSTRACT

Vascularized composite allotransplantation (VCA) is an innovative reconstructive option for patients with complex tissue loss involving the face, upper extremities, and other anatomical structures. This systematic review aimed to synthesize evidence on clinical outcomes, rejection patterns, and immunosuppressive strategies in VCA. A systematic review was conducted following the PRISMA framework. Studies published between 2021 and 2026 evaluating VCA, particularly hand and face transplantation, were identified using relevant keywords and MeSH-related terms, including VCA, hand transplantation, face transplantation, immunosuppression, rejection, and graft survival. VCA provides significant functional, sensory, aesthetic, and psychosocial benefits, contributing to improved daily activities and quality of life. Acute cellular rejection was the most frequently reported immunological complication, particularly during the early post-transplant period. Antibody-mediated and chronic rejection were less common but could contribute to progressive graft dysfunction and loss. VCA offers promising functional and psychosocial outcomes with generally favorable short- to medium-term graft survival. However, rejection and the long-term morbidity associated with lifelong immunosuppression remain major clinical challenges.

Keywords: face transplantation; hand transplantation; immunosuppression; rejection; vascularized composite allotransplantation

How to cite (in APA style)

Sanjaya, I. G. P. H., Hamid, A. R. R. H., Samsarga, G. W., Sudarsa, S. D., Suyata, A. L., & Setiawan, C. W. (2026). Clinical Outcomes, Rejection Patterns, and Immunosuppressive Strategies in Vascularized Composite Allotransplantation: A PRISMA-Based Systematic Review. *Indonesian Journal of Global Health Research*, 8(4), 1409–1416. <https://doi.org/10.37287/ijghr.v8i4.2612>.

INTRODUCTION

Vascularized composite allotransplantation (VCA) refers to the transplantation of multiple tissue types as a single functional unit, and in modern practice it is most often applied to the hand and face. Contemporary reviews describe VCA as the highest available reconstructive option because it uniquely combines motor, sensory, and aesthetic restoration in one intervention (Huelsboemer et al., 2024). The field has grown substantially since the first successful hand transplantation in 1998, and recent syntheses report that around 300–400 VCAs have been performed worldwide, including upper extremity, face, uterus, abdominal wall, penis, and lower-extremity transplants (Woo et al., 2021).

The appeal of VCA is not merely technical; it is deeply functional and psychosocial. In the Korean first hand allotransplantation report, the procedure was presented not only as a surgical success but also as the endpoint of legal, financial, and institutional coordination. At 36 months, the recipient had satisfactory motor and sensory recovery, a DASH score of 23, and a final Hand Transplantation Score of 90, illustrating that VCA can produce durable gains in daily function and quality of life when the program infrastructure is strong (King, 2020). Functional recovery, patient adherence,

rehabilitation, and psychosocial adaptation are also considered essential determinants of long-term reconstructive success in contemporary reconstructive surgery literature (Bohart et al., 2022).

At the same time, VCA is biologically more difficult than standard organ transplantation because the graft contains highly antigenic tissues, especially skin and mucosa. Recent systematic reviews emphasize that VCA requires effective immunosuppression to prevent rejection, yet the standard triple maintenance approach is still commonly adjusted because of nephrotoxicity or persistent rejection risk (Hadidi, 2022). Tacrolimus, mycophenolate mofetil, and prednisone remain the dominant maintenance agents, while sirolimus, everolimus, belatacept, and photopheresis are increasingly used as alternatives or adjuncts in selected cases. Long-term immunosuppression therefore remains one of the major limitations preventing broader implementation of VCA worldwide (Gurtner & Neligan, 2023).

The immunological challenge is particularly important in facial transplantation. Recent reviews found that rejection occurred in 73.3% of face recipients versus 65.9% of hand recipients, while CMV infection was also more frequent after facial transplantation, supporting the view that facial grafts are immunologically more complex because of their mucosal components. Long-term face transplantation studies likewise demonstrate that repeated acute rejection episodes remain common despite modern immunosuppressive protocols (Kantar et al., 2021). These findings have direct implications for graft surveillance, biopsy thresholds, individualized immunosuppressive tailoring, and future development of tolerance-induction strategies in VCA. Therefore, the present systematic review was conducted to comprehensively evaluate the most recent evidence regarding functional outcomes, immunosuppressive strategies, rejection patterns and infectious complications in contemporary VCA practice (Tchiloemba et al., 2021). The novelty of this review lies in its focused synthesis of recent 2021–2026 literature using a PRISMA-based approach while integrating both reconstructive and immunological perspectives across hand and facial transplantation, thereby providing an updated overview of current trends, limitations, and future directions in VCA research. This systematic review aimed to synthesize current evidence regarding clinical outcomes, rejection patterns, and immunosuppressive strategies in VCA.

METHOD

This study was conducted as a systematic review following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) framework. The review focused on studies published between 2021 and 2026 that evaluated vascularized composite allotransplantation (VCA), particularly hand and face transplantation. The primary objective of this review was to synthesize recent evidence regarding functional outcomes, acute and chronic rejection, immunosuppressive strategies and infectious complications to contemporary VCA practice. Because VCA remains an exceptionally rare reconstructive procedure worldwide, the currently available literature is inherently limited in both sample size and methodological uniformity, with most evidence derived from observational case-based studies, registry reports, and review-level synthesis rather than randomized comparative trials.

The literature search strategy was developed according to standard PRISMA principles, including the stages of identification, screening, eligibility assessment, and final inclusion. Five electronic databases were systematically searched: PubMed, SAGE Journals, Cochrane Library, ScienceDirect, and ResearchGate. These databases were selected to maximize capture of both peer-reviewed clinical literature and contemporary review-based evidence related to VCA. Search combinations included the keywords and Medical Subject Heading (MeSH)-related terms “vascularized composite allotransplantation,” “VCA,” “hand transplantation,” “face transplantation,” “composite tissue allotransplantation,” “immunosuppression,” “rejection,” “graft survival,” “vascularized composite transplantation,” and “face allotransplantation.” Boolean operators (“AND,” “OR”) were used to optimize search sensitivity and specificity across databases.

Manual reference screening of included articles was additionally performed to identify potentially relevant studies not captured during the primary database search.

All retrieved records underwent duplicate removal before title and abstract screening. Studies considered potentially relevant subsequently underwent full-text eligibility assessment. Eligibility criteria were intentionally designed to balance comprehensiveness with clinical relevance. Studies were included if they: (1) involved human VCA recipients; (2) focused on hand transplantation, face transplantation, or major reconstructive VCA procedures; (3) reported clinically relevant outcomes including graft survival, rejection episodes, infectious complications, renal toxicity, metabolic complications, psychosocial outcomes, or functional recovery; and (4) were available as full-text articles in English published between 2021 and 2026. Narrative reviews, systematic reviews, clinical reports, cohort studies, and translational reviews were considered eligible because of the limited size of the VCA evidence base. Studies unrelated to reconstructive VCA, animal-only experimental studies, conference abstracts without accessible full text, editorials, commentaries, and non-English publications were excluded from analysis (Figure 1).

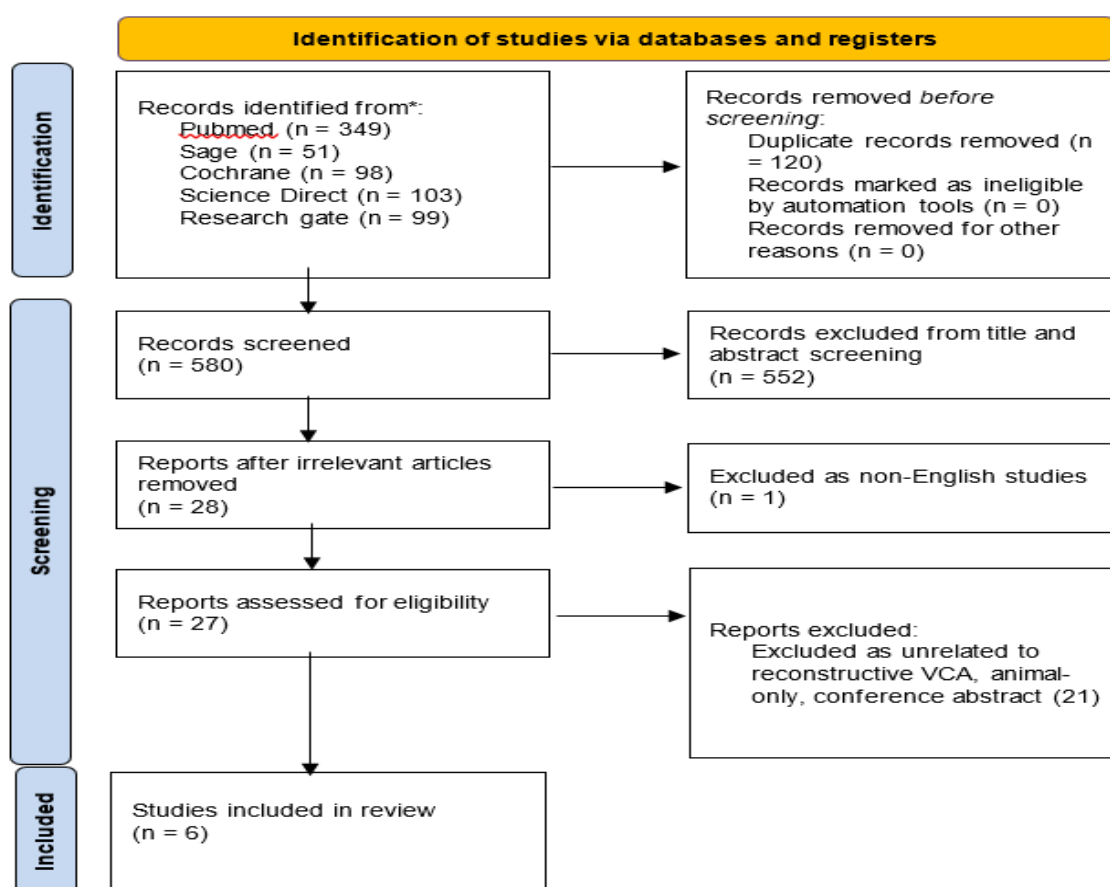


Figure 1. Flowchart of study selection.

Data extraction was performed descriptively because substantial methodological heterogeneity prevented formal quantitative meta-analysis. Extracted variables included study design, year of publication, country or study setting, transplant subtype, immunosuppressive regimen, rejection profile, infectious complications, functional outcomes, and major study conclusions. Risk of bias was assessed qualitatively according to methodological design characteristics, including sample size, comparator availability, duration of follow-up, completeness of outcome reporting, and potential center-specific reporting bias. Single-case reports and uncontrolled observational series were considered to carry higher risk of bias because of limited generalizability and the absence of comparative controls, whereas systematic reviews were considered methodologically stronger but still constrained by heterogeneity and incompleteness of the underlying VCA evidence base.

Because of substantial clinical and methodological heterogeneity across the included studies, findings were synthesized narratively rather than through pooled quantitative meta-analysis.

RESULT

A total of six eligible studies published between 2021 and 2024 were included in this systematic review after PRISMA-based screening and eligibility assessment. Most studies originated from international multicenter literature syntheses rather than prospective clinical cohorts, reflecting the rarity of vascularized composite allotransplantation (VCA) worldwide. Among the included studies, only Woo et al. represented a direct original clinical transplantation report, documenting the first successful hand allotransplantation in Korea with favorable long-term sensory and motor recovery at 36 months after transplantation. The remaining studies consisted predominantly of systematic reviews, narrative reviews, and evidence compendia evaluating facial transplantation, hand transplantation outcomes, long-term graft survival, and immunological complications (Diep et al., 2021). Overall, the currently accessible VCA evidence base remains heavily dependent on retrospective observational reporting and review-level synthesis rather than randomized or prospective comparative trials (Table 1).

Table 1.
General Characteristics of Included Studies

Study (Year)	Study design	Setting	Transplant subtype
(Kim et al., 2021)	Original clinical report	Korea	Hand transplantation
(Diep et al., 2021)	Narrative review / compendium	USA	Facial transplantation
(Tchiloemba et al., 2021)	Systematic review	International	Facial transplantation
(Wells et al., 2022)	Systematic review	International	Hand transplantation
(Milek et al., 2023)	Systematic review	International	Facial and upper-extremity VCA
(Huelsboemer et al., 2024)	Systematic review	International	Face and hand transplantation

Tacrolimus-based triple maintenance therapy consisting of tacrolimus, mycophenolate mofetil (MMF), and corticosteroids remained the dominant immunosuppressive regimen in both hand and facial transplantation. Alternative agents such as sirolimus, everolimus, belatacept, and extracorporeal photopheresis were used selectively in patients with recurrent rejection episodes or immunosuppressive toxicity. Across the included studies, acute rejection remained one of the most frequently reported complications, particularly in facial transplantation, where rejection and CMV infection were consistently reported at higher rates compared with upper-extremity VCA. Infectious complications, including opportunistic viral and bacterial infections, were also recurrently described as major contributors to long-term morbidity following transplantation.^{VI, VII} These findings collectively demonstrate that long-term immunological instability remains a central challenge in modern VCA practice (Table 2).

Table 2.
Immunosuppressive Strategies and Rejection Outcomes

Study	Immunosuppressive regimen	Rejection findings	Infectious complications
(Kim et al., 2021)	Tacrolimus/MMF/steroid-based regimen	No major chronic rejection reported	No major infection emphasized
(Diep et al., 2021)	Standard triple therapy discussed	Acute rejection remained common	Opportunistic infections remained important
(Tchiloemba et al., 2021)	Long-term maintenance therapy summarized	Recurrent acute rejection episodes occurred	Infection associated with chronic immunosuppression
(Wells et al., 2022)	Tacrolimus-based maintenance commonly used	Acute rejection remained frequent	Infection remained a major complication
(Milek et al., 2023)	Multiple regimens summarized	High rejection burden persisted	Infection and metabolic complications were substantial
(Huelsboemer et al., 2024)	Tacrolimus/MMF/steroid dominant; selective sirolimus/belatacept use	Rejection: 65.9% hand vs 73.3% face recipients	CMV infection more frequent in facial transplantation

(Kim et al., 2021) demonstrated excellent long-term functional recovery after hand transplantation, with a DASH score of 23 and a Hand Transplantation Score of 90 at 36 months. Similarly, facial transplantation studies consistently reported improvements in psychosocial integration, speech, facial expression, and quality of life following successful graft survival. However, despite these reconstructive benefits, most studies emphasized that VCA continues to carry substantial long-term clinical burden because of chronic immunosuppression, recurrent rejection episodes, infection risk, and metabolic toxicity. Wells et al. additionally noted that although hand transplantation has matured clinically over the past two decades, the overall evidence base remains limited by small case numbers and heterogeneous reporting between transplant centers. Collectively, the included literature supports the concept that VCA can provide meaningful reconstructive and functional restoration, but its broader clinical expansion remains restricted by immunological and systemic complications (Table 3).

Table 3.
Functional Outcomes and Major Conclusions

Study	Functional outcomes	Major conclusions
(Kim et al., 2021)	DASH score 23; HTS score 90 at 36 months	Successful long-term functional recovery after first Korean hand transplantation
(Diep et al., 2021)	Improved psychosocial and facial function	Facial transplantation feasible but limited by donor scarcity and adverse events
(Tchiloemba et al., 2021)	Generally favorable long-term facial graft outcomes	Long-term feasibility supported despite recurrent rejection
(Wells et al., 2022)	Variable functional recovery across centers	Field matured clinically but evidence remains limited
(Milek et al., 2023)	Functional benefit achievable despite morbidity	Long-term complication burden remains high
(Huelsboemer et al., 2024)	Functional restoration achievable in face and hand transplantation	Rejection and immunosuppressive toxicity remain dominant barriers

The overall methodological quality of the included studies was limited primarily by retrospective design, low case volume, and dependence on observational reporting. The single clinical case report by Woo et al. was categorized as high risk of bias because of the absence of comparator groups and the highly center-specific nature of follow-up outcomes. In contrast, the systematic reviews demonstrated stronger methodological structure, although they remained constrained by heterogeneous source data, inconsistent follow-up duration, and incomplete global case capture. Recent reviews also explicitly acknowledged that not all published VCA cases could be comprehensively identified and that long-term updates from transplant centers were inconsistently available. Consequently, the present evidence base should still be interpreted cautiously, and future multicenter prospective registries will be necessary to improve the reliability and comparability of VCA outcome reporting (Table 4).

Table 4.
Risk of Bias Assessment

Study	Risk of bias	Explanation
(Kim et al., 2021)	High	Single-case report with no comparator
(Kantar et al., 2021)	Moderate	Narrative review without controlled comparison
(Tchiloemba et al., 2021)	Moderate	Heterogeneous source studies and variable follow-up
(Abud et al., 2022)	Moderate	Sparse observational evidence base
(Milek et al., 2023)	Moderate	Significant heterogeneity across graft types and centers
(Huelsboemer et al., 2024)	Moderate	PRISMA-based methodology but incomplete global case capture

DISCUSSION

Vascularized composite allotransplantation (VCA) remains one of the most ambitious reconstructive procedures because it can restore both function and appearance in patients with catastrophic tissue loss (Knoedler et al., 2026). The first hand allotransplantation reported from Korea showed that this is achievable when surgical expertise is supported by legal approval,

funding, rehabilitation, and public acceptance, and the recipient achieved satisfactory long-term recovery with a DASH score of 23 and a Hand Transplantation Score of 90 at 36 months. More broadly, recent field-level reviews note that VCA is still rare worldwide, with fewer than 400 procedures performed globally, which explains why the evidence base remains small and center-specific (Brandacher et al., 2025).

Despite these encouraging functional results, rejection remains the major biological barrier. The 2022 systematic review of hand transplantation found 96 patients with 148 hand transplants, with 57 patients experiencing acute rejection and 5 chronic rejection, showing that rejection is still common even in experienced programs. The 2024 systematic review of face and hand transplantation also reported that tacrolimus was used in 97.8% of face-transplant patients, with mycophenolate mofetil in 95.6% and steroids in 73.3%, yet rejection still occurred in 65.9% of hand recipients and 73% of face recipients.

Face transplantation appears to carry an even greater immunological burden than hand transplantation. Recent reviews emphasize that facial grafts are more complex because they include highly antigenic tissues and mucosa, which makes immune surveillance and rejection control more difficult than in extremity grafts. The 2024 review also notes that acute rejection remains highly prevalent in VCA overall, reaching up to 89% in pooled recipient data, and this high rejection burden is one reason why facial VCA requires especially close follow-up (Hehir et al., 2026).

Because of this persistent rejection risk, VCA management increasingly depends on individualized immunosuppression rather than a single universal regimen. The 2024 immunosuppression review shows that standard triple therapy is often adjusted because of nephrotoxicity or rejection, and alternative strategies such as sirolimus, everolimus, belatacept, and photopheresis are used when conventional therapy becomes inadequate or toxic. This pattern supports the idea that future gains in VCA will likely come from more targeted immunomodulation rather than simply increasing the intensity of systemic therapy (Dandoulakis, 2025).

The main limitation of the current literature is that it remains heterogeneous, incomplete, and heavily observational, so conclusions must remain cautious. The recent field review explicitly states that standardized reporting is still lacking, patient-reported outcome measures remain heterogeneous, and the rarity of the procedure limits cross-study comparison and pooled inference (Chakradhar et al., 2026). The strength of this review is that it focuses on recent free full-text literature and keeps the interpretation closely aligned with what the evidence can genuinely support, but its limitation is that the available studies are still too few and too diverse to justify firm comparative claims across graft types or protocols (Zhang et al., 2023). Future research should prioritize multicenter prospective registries, standardized outcome measures, longer follow-up periods, and collaborative international databases to improve statistical power and permit more reliable comparisons between immunosuppressive strategies and graft-specific outcomes. In addition, further investigation into tolerance-induction protocols, biomarker-guided rejection surveillance, and less toxic immunomodulatory therapies will be essential to improve long-term graft survival and patient safety in VCA (Longo et al., 2025).

CONCLUSION

Vascularized composite allotransplantation is a highly effective but highly complex reconstructive strategy that can restore function, appearance, and quality of life in selected patients. The recent literature shows consistent benefit, but also persistent rejection, infection, renal toxicity, and the need for lifelong immunosuppression. The next phase of VCA research should prioritize tolerance-induction, graft-specific immunosuppression, multicenter registries, and standardized outcome reporting so that the field can move from rare success stories toward reproducible international practice.

REFERENCES

- Abud, T., Kounidas, G., Martin, K. R., Werth, M., Cooper, K., & Myint, P. K. (2022). Determinants of healthy ageing: a systematic review of contemporary literature. *Aging Clinical and Experimental Research*, 34(6), 1215–1223. <https://doi.org/10.1007/s40520-021-02049-w>
- Bohart, S., Møller, A. M., Andreassen, A. S., Waldau, T., Lamprecht, C., & Thomsen, T. (2022). Effect of Patient and Family Centred Care interventions for adult intensive care unit patients and their families: A systematic review and meta-analysis. *Intensive & Critical Care Nursing*, 69, 103156. <https://doi.org/10.1016/j.iccn.2021.103156>
- Brandacher, G., Messner, F., Al-Salmay, Y., & Kaufman, C. L. (2025). Clinical manifestation, mechanisms, and potential targets of intervention for chronic rejection in vascularized composite allotransplantation. *Transplantation*, 109(11), 1710–1722.
- Chakradhar, A., Yu, M., & Talbot, S. G. (2026). Systematic review of emerging technologies in vascularized composite allotransplantation. *Frontiers in Transplantation*, 5, 1760147.
- Dandoulakis, E. (2025). Immunomodulatory therapies to prevent transplant rejection in composite tissue allotransplantation: Current status and future prospects. *Available at SSRN 5523661*.
- Diep, G. K., Berman, Z. P., Alfonso, A. R., Ramly, E. P., Boczar, D., Trilles, J., Colon, R. R., Chaya, B. F., & Rodriguez, E. D. (2021). The 2020 facial transplantation update: a 15-year compendium. *Plastic and Reconstructive Surgery Global Open*, 9(5), e3586.
- Gurtner, G. C., & Neligan, P. C. (2023). *Plastic surgery E-book: volume 1 principles*. Elsevier Health Sciences.
- Hadidi, A. T. (2022). Plastic surgery principles. In *Hypospadias Surgery: An Illustrated Textbook* (pp. 323–333). Springer.
- Hehir, C. M., O'Connor, M., Marinescu, I., Dengu, F., Giele, H. P., & Dolan, R. T. (2026). Vascularised composite allotransplantation: emerging applications in reconstructive surgery and solid organ transplantation. *Medicina*, 62(2), 245.
- Huelsboemer, L., Boroumand, S., Kochen, A., Dony, A., Moscarelli, J., Hauc, S. C., Stögner, V. A., Formica, R. N., Pomahac, B., & Kauke-Navarro, M. (2024). Immunosuppressive strategies in face and hand transplantation: a comprehensive systematic review of current therapy regimens and outcomes. *Frontiers in Transplantation*, 3, 1366243.
- Kantar, R. S., Alfonso, A. R., Diep, G. K., Berman, Z. P., Rifkin, W. J., Diaz-Siso, J. R., Sosin, M., Gelb, B. E., Ceradini, D. J., & Rodriguez, E. D. (2021). Facial transplantation: principles and evolving concepts. *Plastic and Reconstructive Surgery*, 147(6), 1022e-1038e.
- Kim, D.-H., Ahn, J., Kang, H. K., Kim, M.-S., Kim, N.-G., Kook, M. G., Choi, S. W., Jeon, N. L., Woo, H.-M., & Kang, K.-S. (2021). Development of highly functional bioengineered human liver with perfusable vasculature. *Biomaterials*, 265, 120417.
- King, T. W. (2020). Plastic surgery. In *Building a clinical practice* (pp. 203–214). Springer.
- Knoedler, L., Niederegger, T., Schaschinger, T., Hundeshagen, G., Munzinger, R., Heiland, M., Cetrulo, C. L., & Lellouch, A. G. (2026). A systematic review of treatment strategies to combat acute and chronic rejection episodes in vascularized composite allotransplantation. *Frontiers in Immunology*, 17, 1733221.
- Longo, B., Pistoia, A., D'Orsi, G., & Cervelli, V. (2025). Mechanisms of rejections and tolerance strategies in vascularized composite allotransplantation: a comprehensive review. *Plastic Reconstructive and Regenerative Surgery*, 71–80.
- Milek, D., Reed, L. T., Echternacht, S. R., Shanmugarajah, K., Cetrulo Jr, C. L., Lellouch, A. G., Langstein, H. N., & Leckenby, J. I. (2023). A systematic review of the reported complications related to facial and upper extremity vascularized composite allotransplantation. *Journal of Surgical Research*, 281, 164–175.
- Tchiloemba, B., Kauke, M., Haug, V., Abdulrazzak, O., Safi, A.-F., Kollar, B., & Pomahac, B. (2021). Long-term outcomes after facial allotransplantation: systematic review of the literature. *Transplantation*, 105(8), 1869–1880.
- Wells, M. W., Rampazzo, A., Papay, F., & Gharb, B. B. (2022). Two decades of hand transplantation: a systematic review of outcomes. *Annals of Plastic Surgery*, 88(3), 335–344.
- Woo, S. H., Kim, Y. W., Cheon, H.-J., Jang, S., Do, J.-Y., Choi, J. H., Kang, D. H., Nam, H. J.,

- Yoo, M. J., & Lee, Y. S. (2021). Process of obtaining social consensus and 3-year functional outcomes of the first hand allotransplantation in Korea. *Journal of Korean Medical Science*, 36(2).
- Zhang, L., Hoyos, I. A., Zubler, C., Rieben, R., Constantinescu, M., & Olariu, R. (2023). Challenges and opportunities in vascularized composite allotransplantation of joints: a systematic literature review. *Frontiers in Immunology*, 14, 1179195.