

Peer Review File

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Reviewer A

The authors performed a systematic review on robotic-assisted LVA surgery. This is a well written review about currently published studies in this field. I have the following suggestions.

1. Anastomotic patency rates and if available complications and adverse events should be added for the different studies cited.

Reply: We appreciate the insightful feedback. This is important and comparable information and clarifications have been made accordingly in the results tables.

2. For a more balanced view images of both currently available systems should be added

Reply: The submitted image was thought to serve as an example of a robotic system in general, but separate images of the different systems would indeed be better. Images of both systems have been included.

Reviewer B

Overall, this paper provides a good overview of the emerging use of robotics in lymphaticovenous anastomosis surgery for lymphedema treatment. The introduction establishes the rationale for exploring robotic LVA by reviewing the basics of lymphedema and LVA surgery, and how robotics can help overcome limitations in human dexterity.

In the discussion, the paper delivers a balanced narrative of the potential benefits and limitations of robotic LVA based on the current evidence. The main benefits highlighted are improved precision and accuracy, tremor filtration, articulating instruments for hard-to-reach areas, a steep learning curve, and making complex microsurgery more accessible. The limitations discussed include longer surgery times, costs, and lack of haptic feedback.

Some suggestions for improving the paper:

Introduction:

Provide more details on the surgical principles and technical challenges of LVA surgery to establish why robotics has promise in this application.

Reply: We would like to express our sincere gratitude for the insightful comments. The delicate nature of lymphatic surgery has been further elaborated on in the introduction (line 111-114), as suggested.

Methods:

What study designs were included?

Provide more specifics on the data extraction process - what key data/variables were obtained

from the selected studies?

Were studies screened by more than one author?

Reply: All study designs were included; this has been clarified on row 166. The extraction process has been addressed on rows 167-169.

Results:

The results should be expanded to include more specific information from the included studies.

Where were the studies performed?

What were the patient populations?

What were the main outcomes reported?

Reply: This is important for the whole of the manuscript. The results have been elaborated on as per suggestion, see tables 3-4.

Discussion:

Given the limited evidence base, discuss the preliminary nature of the findings and need for larger clinical studies.

Expand on the comparison of the different robotic systems used in the studies.

Address generalizability - what patient populations/lymphedema etiologies have been studied so far? How might this impact adoption?

Spend more time on the cost/health economics implications given the concerns about high costs acting as a barrier to adoption.

Reply: We are grateful for the perceptive comments and have made adjustments accordingly. The limited nature of the data to date has been discussed further, including the need for larger studies. We also touched on the fact that further studies need to be more nuanced including investigating the effect of robot assistance for surgeons with different levels of proficiency with microsurgery. The generalizability has also been addressed further, including the view that the robotic LVA can be seen as a first foundational step before translating the technique to more complex procedures (row 301-309). Regarding cost of implementation, further searches have not yielded anything specific for the implementation of robot assistance in LVA surgery, which is why we've chosen the implementation of the da Vinci system as an illustration (row 253-264).

Conclusions:

Discuss specific future research directions beyond just "larger clinical studies" - head-to-head robotic system comparisons, long-term outcomes, cost-effectiveness studies etc.

Strengthening the above areas would improve the academic value of this article.

Reply: This is of paramount importance and these points have been further elaborated on in the end of the discussion (row 314-318)

Reviewer C

Introduction: well written and comprehensive

Methods:

General comment: The search strategy seems well-thought-out and robust, designed to capture a comprehensive set of relevant studies for the topic in question.

Specific remarks:

Considering potential improvements could enhance the breadth and quality of the systematic review or literature search results such as:

- Database Coverage: While the chosen databases are comprehensive, the inclusion of additional databases or grey literature sources (e.g., conference proceedings, theses) could potentially uncover more relevant studies, especially in a niche area like robotic LVA surgery.

-Risk of Bias Assessment: While not explicitly mentioned in your description, an assessment of the risk of bias in included studies is crucial for understanding the quality and reliability of the evidence.

Could you please provide further clarification on the previously mentioned points?

Reply: First of all, we want to acknowledge that these comments have provided us with valuable insights that has improved the quality of our manuscript. The databases were chosen as they were judged to be most likely to contain publications on the topic. The topic of bias is a very important one, and a comment on this has been added to the discussion, see row 203-204.

Results:

General comment: The included studies directly address the research question concerning the use of robotic assistance in lymphovenous anastomosis (LVA) surgery, specifically focusing on outcomes like quality of life, anastomosis time and patency, and learning curves. This aligns well with the search terms and the focus on robotic surgical procedures and microsurgery outlined in the search strategy.

Specific remark: The results section presents individual study findings but does not offer a quantitative synthesis or meta-analysis, (which might be due to the heterogeneity of study designs and outcomes). A more detailed analysis or discussion on the cumulative evidence could enhance understanding of the overall effectiveness and efficiency of robotic-assisted LVA surgery. Could you provide this evidence in your manuscript?

Reply: As commented, the studies vary greatly regarding methodology, outcomes reported and general focus, which is why we elected to not perform any meta-analysis or quantitative statistics. The reasoning behind this has been clarified on rows 167-169.

Discussion:

General comment: The discussion critically examines the benefits and drawbacks of robotic systems, including cost considerations, the learning curve associated with their use, and the lack of haptic feedback. this is crucial for understanding the nuanced nature of implementing such technologies in clinical practice.

Specific remark: While the discussion covers the benefits of robotic systems broadly, a more detailed comparison between the MUSA and Symani systems, informed by direct comparative studies, would provide valuable insights into their relative strengths and weaknesses. why is this OMITTED? if available please include in your manuscript.

Reply: This is an important aspect, but there are no available studies on the subject to date.

The point has, however, been added as a suggestion for future research (row 317-318).

Reviewer D

Surgical treatments of lymphedema – a literature review on robot-assisted LVA GS-24-22

The surgical performance in lymphatic microsurgery requires precision and dexterity of the human hands. Robotic supermicrosurgery facilitates for the performance of LVAs supplying tremor amortization and motion scaling up to 20x. This may lead to increased precision. The absence of haptic feedback and the need for the performing surgeon to develop a “see-feel” concept require an adequate training (1). Unfortunately, this approach is only available in centres that can afford the technology and have specially trained surgeons.

To date, the main limitations to diffusion of this approach are the steep learning curve, and cost optimization.

The author should suggest a solution to these problems (European Training Center? other?)

1. Gousopoulos E, Grünherz L, Giovanoli P, Lindenblatt N. Robotic-assisted microsurgery for lymphedema treatment. *Plast Aesthet Res* 2023;10:7. <http://dx.doi.org/10.20517/2347-9264.2022.101>

Reply: We are grateful for the insightful observations. This is an excellent point and like any highly specialized type of intervention, the technique is dependent on appropriate training and equipment. A comment has been added on the topic, see rows 285-288, as suggested.

Reviewer E

The authors conducted a review of the results of robotic-assisted LVA. This technology is designed to help surgeons with physiological tremor problems perform super microsurgical anastomosis and challenging surgical fields such as the intra-abdominal area.

To improve the presentation, I have some recommendations:

- First, in the results section and Table 3, please provide more details about the statistical results of each study.
- Secondly, could you provide information about the learning curve or training sessions required before using the microsurgical robotic systems on patients?
- Finally, please discuss the advantages and disadvantages of the microsurgical robotic system and provide your opinion on when it should be used."

Reply: We appreciate the time that has gone into reviewing our work. Due to the nature of the studies included, including two case series where comparative statistics were not the focus, and the fact that the remaining studies compared different variables, we've elected to exclude specifics on the statistical methods. The results section, however, has been expanded to provide

more specific details from the included studies.

Although van Mulken et al (2022) specify the amount of training that the surgeon performing the operations had before starting the study, the included studies reported no specifics on the training regimen they used before using robotic systems for actual patient cases. For general comments on the learning curve, see row 266-288.

As the implementation of robotics in LVA surgery is still in its infancy, it is difficult to suggest criteria for use at this point. We have, however, elaborated on potential situations where robot assistance might be beneficial, see row 294-309.

Reviewer F

The article is very interesting and important. The reviewer thinks it is worth being published, however, there is a minor revision before being published.

Line 107-109; It looks like that some revisions have been made before submitting. It seems that this sentence is left being not deleted.

Reply: We are grateful for this observation and have addressed it accordingly,

Reviewer G

This is an interesting revision about the role of robotic microsurgery applied to LVA. Inclusion and exclusion criteria are right, but results are poor. There is a kind of mistake in line 107 that seems to be apart of the work. You need to explain tables. Discussion is acceptable.

In general, this work must be rewritten, removing the previously indicated paragraph as well as improving results descriptions.

Reply: We extend our appreciation for the helpful critique that has helped us improve the quality of our manuscript. The results are presented mostly in table format and this section has been totally rewritten as per suggestion to include more specific results from each individual paper, see table 3-4.

Reviewer H

This review on robotic microsurgery presents an abstract enumeration of the contents of each paper, leaving an impression of a lack of novelty and clinical significance. However, there is potential for improvement to make the paper more valuable, as outlined below:

This review appears to simply list the reports of each paper, with repetitive content and lacking consistency in presentation, making it somewhat difficult to read. It would be clearer to organize the content by “specific categories” such as anastomosis time and patency rate, present the results of each paper with organized P-values and sample sizes, and then provide discussions based on these data. Additionally, using figures and tables to illustrate comparisons,

such as anastomosis time, would enhance readability.

In general, the expressions are too abstract, and presenting more numerical data would enhance persuasiveness. This applies to Table 3 as well, where adding concrete numerical data would be beneficial. For example, in lines 118-119, specific numerical values and P-values are provided, which are highly beneficial for lymphatic surgeons. Including such specific numerical data throughout the paper would enhance its persuasiveness.

Reply: We value the rigorous critique and constructive suggestions. The tables where the main results are presented have been totally rewritten, see table 3-4. Due to the large span of focus for the included paper there was a lack of consistency in the parameters reported, which is why we elected not to perform any meta-analysis or quantitative statistics.

The incidence rate of angiosarcoma at 10% seems somewhat too high. Considering the estimated population of lymphedema patients mentioned in this paper, which is around 100 to 200 million, having 10% of this population developing angiosarcoma appears excessive from a clinical perspective. It is recommended to use a more conservative expression.

Reply: This sounds very reasonable, and the wording has been adjusted as suggested, see row 56.

When considering the additional costs associated with using robotics, if the clinical outcomes of robot-assisted surgery are equivalent to those achieved with manual anastomosis and do not demonstrate significant superiority, it may be difficult to justify the utility of robotic surgery. If results comparing the hand-sewn and the robotic-sewn were not significant, then ultimately, it may be more cost-effective to perform manual anastomosis without the preparation time required for robotics. The merits of robotic surgery is overestimated in this paper.

For instance, in the study by Bardon in Table 3, with N=22, the anastomosis time using robot-assisted technique (25.3 ± 12.3 min) was significantly longer than hand-sewn (14.1 ± 4.3 min; $p < 0.01$), suggesting the potential superiority of hand-sewn techniques. It would be beneficial to further discuss points where robotic surgery may be inferior.

Reply: While very valid points, the aim of the included studies have been to prove the feasibility rather than the superiority of robot assistance at this point and the studies are far too small to draw any final conclusions. This is however an excellent point and the reasoning has been elaborated on in the discussion, see rows 294-296.

Personally, I am interested in aspects such as the time required for robotic setup.

Reply: This is an important aspect in the day to day practice, but unfortunately the included studies do not comment on setup time specifically.

Overall, enhancing the specificity of numerical data and organization of the content would greatly improve the persuasiveness and readability of the paper.

Reviewer I

nicely written, straightforward, systematic review of this emerging topic.

need to delete the instructional text in the 3. Main body heading

Reply: We appreciate the valuable feedback and have made changes according to the suggestion.

Reviewer J

I commend the authors for a timely literature review. Following suggestions should help refine and update the manuscript, ensuring its accuracy and contemporary relevance as well as broadening the scope and depth of the discussion, particularly in relation to the evolving field of supermicrosurgery and the role of robotic technology.

1) It is important to clarify that primary lymphedema is not an uncommon condition, as is well understood by experienced lymphologists. The primary issue lies in its under-diagnosis. I suggest reframing this point in your paper to avoid perpetuating the misconception of its rarity.

Reply: Firstly, we want to acknowledge the time and effort that has gone into reviewing our manuscript and convey our appreciation for the constructive feedback that will undoubtedly enhance our work. It is important to be correct with these matters and the language of the paragraph has been changed accordingly, see row 48-53.

2) The description of Lymphatic-Venous Anastomosis (LVA) as merely a "shunt" oversimplifies its mechanism. Recent observations by surgeons indicate broader systemic effects that extend beyond the shunt mechanism. These include humoral effects and a cascade of biochemical reactions initiated by the communication between lymphatic and venous systems. I recommend referencing the study by Imai H et al. in *iScience* (2023), which provides insight into the peripheral T cell changes post-LVA, to substantiate this point.

Reply: The publication by Imai and colleagues is indeed an interesting read. Although the scope of our manuscript is not the pathophysiology of lymphedema, we agree that the shunt analogy is over simplistic in this context. Comments have been made accordingly and Imai et al has been added to the references, see row 109-110.

3) The assertion regarding the physiologic tremor range of 0.5 – 3 mm being a limiting factor for supermicrosurgeons is outdated and does not reflect the capabilities of well-trained practitioners in this field. The referenced 1956 study does not represent the skill level of contemporary supermicrosurgeons, for whom managing tremors of 0.5 mm and above is relatively straightforward. The challenge increases significantly with vessels smaller than 0.3 mm, and vessels of 0.1 mm remain a challenge even for the most skilled. It would be beneficial to update this information to prevent misconceptions about the feasibility of supermicrosurgery among trainees.

Reply: The reference is thought to be an illustration of the difficulty faced by the microsurgeon and not to serve as a deterrent for aspiring colleagues, which is an important aspect. This has been elaborated on in the discussion, see row 212-215.

4) In the studies you referenced concerning robotic assistance in surgical procedures, a critical

observation is the absence of standardization for the varying experience levels of surgeons. This oversight is significant as the perceived benefits of robotic assistance are highly contingent on the surgeon's expertise, with less experienced surgeons typically deriving greater advantage from the technology. It would be beneficial for your paper to acknowledge and explore this factor, offering a more nuanced and thorough analysis of how robotic assistance impacts surgical outcomes across different skill levels.

Reply: This is a central aspect in the reasoning behind robot assistance and there is some data on the subject. To clarify the reasoning, we've expanded on the reference by Frieberg et al. on the learning curve of robotic microsurgery, see row 272-284.

5) The paper should emphasize that LVA serves as a foundational step in the progression of supermicrosurgery. The critical value lies not just in the application of robotics to LVA but in the potential for robotics to facilitate more advanced procedures, such as in brain lymphatics. Highlighting LVA as a proving ground for robotic technology in more complex supermicrosurgical contexts would offer a more forward-looking perspective on the subject.

Reply: Again, an excellent point that has now been addressed in the discussion, see row 301-309.