Original Article

Lymphaticovenular Anastomosis for Patients with Lymphedema of the Lower Extremity: A Cumulative Experience at Siriraj Hospital

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Background: Lower extremity lymphedema is a chronic disturbing condition that commonly results from cancer or cancer treatment. Lymphaticovenular anastomosis (LVA) is one of the most effective lymphedema operations. Over eight years of data collection, almost a hundred lower extremity lymphedema patients underwent LVA operations at Siriraj Hospital.

Objective: To summarize the attributes of lower extremity lymphedema patients treated by the LVA operation at Siriraj Hospital, and to assess their surgical treatment outcomes.

Materials and Methods: The present study employed a single-center retrospective review to evaluate the characteristics and outcomes of lower extremity lymphedema patients that underwent LVA operations between 2010 and 2018 at Siriraj Hospital. The reduction of limb circumference and the cellulitis rate was intended to measure the LVA operation's effectiveness by using descriptive (SPSS) statistics.

Results: Ninety-four lower extremity lymphedema patients underwent the LVA operation. The average number of anastomosis was 2.9±1.2. The post-operative circumferential reductions were 4.3±1.8 cm (84.3%) at 10 cm above the patella and 5.3±0.9 cm (89.8%) at 10 cm below the tibial tuberosity. Episodes of cellulitis were consistently decreased from 1.9±0.3 to 0.6±0.1 times per year. Among the non-surgical treatments, 69.1% of the lymphedema patients were treated with pressure garments. However, only 6.4% of those patients applied skincare.

Conclusion: LVA is an effective operation for lower extremity lymphedema. LVA can satisfactorily reduce excessive lymphedematous tissues and cellulitis episodes. According to the cumulative data of LVA at Siriraj Hospital, the outcome of LVA in the lower extremity has an acceptable outcome. The same holds true for the upper extremity. Unfortunately, some patients disregarded the surgical treatment. There should be an effective healthcare team to encourage this valuable treatment practice.

Keywords: Lymphedema; Lower extremity lymphedema; Lymphaticovenular anastomosis; LVA; Supermicrosurgery

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Lymphedema is one of the most debilitating and disturbing conditions that affect patient lives. Due to an excessive accumulation of protein-rich fluid in interstitial spaces, it causes swelling and fibrosis of tissues, especially in the extremities[1]. Lower extremity lymphedema is more disturbing than upper extremity lymphedema because of the high infection rate in the lower extremity[2]. There are various causes of lower extremity lymphedema, which can be classified into primary and secondary lymphedema. Primary lymphedema results from intrinsic malformations or genetic abnormalities in the lymphatic system. In contrast to primary lymphedema, secondary lymphedema occurs because of trauma, infection, or malignancy[3]. Because of improvement in cancer treatment, the survival rate of oncological patients has significantly increased, and this has resulted in higher numbers of lymphedema patients[4]. In the oncologic population, extensive lymph node removal[5], receipt of adjuvant chemotherapy/radiotherapy[6], and a higher body mass index (BMI)[7] are identified as potential risk factors for lymphedema. The other common causes

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of secondary lower extremity lymphedema involve diverse types of infection, such as filariasis, repetitive infection, and post-traumatic soft tissue injury[3,8].

Lymphedema severely affects patients' quality of life. This is because of their physical inability and their psychological distress. Lymphedema experts have attempted to develop treatments to overcome these problems. First, non-surgical treatment is necessary for all lymphedema patients. It is an initiative and mainstay treatment that includes manual lymphatic drainage, decongestive lymphatic therapy, and skin care[9]. Secondly, surgical treatment is indicated for persistent lymphedema or recurrent infections[10]. Lymphaticovenular anastomosis (LVA) is a microscopic operation that generates an effective channel to bypass excessive fluid from the lymphatic to the venous system. Mihara et al (2016) analyzed the effectiveness of LVA in lower-limb lymphedema and revealed that LVA can decrease the limb circumference by a maximum of 80.0% and decrease the mean occurrence of cellulitis from 0.89 to 0.13 times per year[11].

Although the LVA operation has been performed at Siriraj Hospital in Thailand since 2010, an analysis of patient's characteristics and success rate following this procedure had not previously been systematically documented. Accordingly, the present study aimed to summarize the attributes of lower extremity lymphedema patients treated by the LVA operation at Siriraj Hospital, and to assess their surgical treatment outcomes. The findings of the present study would contribute to the development of the lymphedema healthcare system.

Materials and Methods

The present study was a retrospective study approved by the Institutional Review Board (SiRB) of Siriraj Hospital, under protocol number 912/2561. The present study included 94 lower extremity lymphedema patients who underwent the LVA operation at the Department of Surgery, Siriraj Hospital, Mahidol University, between January 1, 2010 and August 31, 2018.

Pre-operative evaluation

Lymphedema-suspected patients were investigated by lymphoscintigraphy (^{99m}Tc-dextran lymphoscintigraphy) to confirm the diagnosis. The patients who had negative lymphoscintigraphy results were reinvestigated by a fluorescent lymphangiogram with indocyanine green (ICG), which is more sensitive to lymphedema.

Surgical techniques

To identify the lymphatic vessels, the surgeon started with an injection of 1% isosulfan blue or ICG in the intradermal or subcutaneous layers of the first and second webspace for 0.1 ml in each area. After that, a handheld ICG camera (FLUOBEAM®, Fluoptics Co., Grenoble, France) was used to locate the lymphatic vessels and to determine the incision. In the authors' practice, a duration between ICG injection and surgical site identification was approximately 10 minutes. Prior to performing the incision, which was typically about 2.5 to 4 cm, lidocaine with epinephrine was injected into the area for local anesthetic effect. However, general anesthesia was an alternation of the anesthetic method if the patient was concerned. Then, an operative microscope (OPMI Pentaro 900 and OPMI Vario S88 system, Carl Zeiss Co., Jena, Germany) was applied to identify the lymphatic vessels and nearby venules.

At Siriraj Hospital, plastic surgeons accessed the vessels in the subcutaneous and suprafascial layers to get larger diameters of the vessels, compared to other layers. Finally, the lymphatic vessels and the venules were connected with end-to-end, end-to-side, or side-to-side techniques. The anastomoses were evaluated by the Acland test or the dynamic ICG lymphography test to confirm their patency.

Postoperative care

After the operation, the lymphedema patients were recommended to continue decongestive lymphatic therapy or other non-operative treatments starting two weeks after the operation to prevent anastomosis failure.

Outcome measurements

A circumference reduction of the affected limbs after the LVA operation was considered as the primary outcome. The circumference of the limbs was measured at 10 cm above the patella and 10 cm below the tibial tuberosity at least three times, at pre-operation, six months after the operation, and during the last visit to the lymphedema clinic. The efficacy of circumference reduction was presented as reduction rate, which was described below. The secondary outcome was episodes of cellulitis.

$$\text{Reduction rate} = \frac{\text{Circumferential reduction}}{\text{Pre-operative circumferential difference}} \times 100$$

Circumferential reduction = pre-operative circumference of effected leg – post-operative circumference of effected leg

Pre-operative circumferential difference = circumference of effected leg – circumference of normal leg

Statistical analysis

The data were operated by descriptive statistical analysis under SPSS. Types of data, including the patients' demographic data, lymphedema characteristics, and non-surgical treatment of lymphedema were presented as frequencies and percentages. The outcomes of the LVA operation, which included the limb circumference and episodes of cellulitis, were analyzed by a paired t-test, at a p-value less than 0.05. The results also demonstrated mean scores and standard deviations (SD).

Results

Between 2010 and 2018, the LVA was regarded as the supermicrosurgery era at Siriraj Hospital. The patients' characteristics are shown in Table 1. Their average age was 52.3±14.6 years, ranging from 10 to 79 years. Female was significantly found up to 92.6% of all patients. The patients' average BMI was 25.1 kg/m², which qualified as obesity, according to the Asia-Pacific BMI classification. Other comorbidities involved hypertension, diabetes mellitus, and dyslipidemia.

Causes of lower extremity lymphedema were categorized as primary and secondary lymphedema, at 12.8% and 87.2%, respectively. For secondary lymphedema, gynecologic malignancy was the largest group, which included cervical cancer (52.1%) and endometrial cancer (16.0%). The present study revealed the association between lymphedema and cancer-related operative treatments including total abdominal hysterectomy with bilateral salpingo-oophorectomy (TAH with BSO) (59.6%), chemotherapy (26.6%), radiation therapy (48.9%), and brachytherapy (25.5%).

Once malignancy was diagnosed, the patients' mean duration of the clinical lymphedema before initiating the malignancy treatment was approximately 7.8±2.0 years. Since the patients had developed clinical lymphedema prior to their first visit to the lymphedema clinic, the average duration was 6.9±3.1 years. The duration of the follow-up after the LVA operation ranged from 10 to 87 weeks with a median of 29.5 weeks.

The characteristics of lymphedema are shown in Table 2. Most patients were in the early stage of Campisi's lymphedema staging (61.7%). Up to one-third of the patients (27.7%) had a history of cellulitis. Most of the lymphedema patients (69.1%) were treated with pressure garments as a non-surgical treatment concurrently with the LVA operation. Other non-surgical treatments are compression bandage (9.6%), twisting tourniquet decongestive therapy (7.4%), manual lymphatic drainage (2.1%), and pneumatic pump (1.1%). On the other hand, only six patients (6.4%) routinely applied skin care.

LVA was performed under local anesthesia in 56 cases and under general anesthesia in 38 cases.

Table 1. Demographic data

Demographic data	n=94
Age (years); mean±SD	52.3±14.6
Sex; n (%)	
Male	7 (7.4)
Female	87 (92.6)
BMI (kg/m^2); mean±SD	25.1±5.1
Follow-up (weeks); mean±SD	33.0±21.3
Median of Follow-up (weeks); median (IQR)	29.5 (10 to 87)
Onset after cancer therapy (years); mean±SD	7.8±2.0
Duration of lymphedema (years); mean±SD	6.9±3.1
Side; n (%)	
Right	39 (41.5)
Left	55 (58.5)
Underlying disease; n (%)	
DM	5 (5.3)
Hypertension	17 (18.1)
Dyslipidemia	8 (8.5)
Heart disease	1 (1.1)
Cause of lymphedema; n (%)	
Cervical cancer	49 (52.1)
Endometrial cancer	15 (16.0)
Primary lymphedema	12 (12.8)
Others diagnosis	18 (19.1)
Cancer treatment; n (%)	
TAH with BSO	56 (59.6)
Pelvic node dissection	2 (2.1)
Groin node dissection	6 (6.4)
Others surgery	6 (6.4)
Chemotherapy	25 (26.6)
Radiation therapy	46 (48.9)
Brachy therapy	24 (25.5)

SD=standard deviation; IQR=interquartile range; DM=diabetes mellitus; BMI=body mass index; DM=diabetes mellitus; TAH with BSO=total abdominal hysterectomy with bilateral salpingo-oophorectomy

Table 2. Characteristics of lymphedema

	n (%)
Campisi's lymphedema stage	
Early stage (I, II)	58 (61.7)
Late stage (III-IV)*	36 (38.3)
Previous cellulitis	26 (27.7)

* No stage V

Table 3. Intraoperative findings

Type of anesthesia; n (%)	
General	38 (40.4)
Local	56 (59.6)
Operative time (minutes); median (IQR)	210 (60 to 405)
Number of anastomosis; mean±SD	2.9±1.2
Lymphatic vessel diameter; mean±SD	0.7±0.3

SD=standard deviation; IQR=interquartile range

The average operative time was 210 minutes, with a range of 60 to 405 minutes. The average number of anastomosis was 2.9±1.2 and the average vessel diameter was 0.7±0.3 mm (Table 3). The outcomes of the LVA operation are shown in Table 4 and 5. The mean circumferences reduction was 4.3±1.8 cm at 10 cm above the patella and 5.3±0.9 cm at 10 cm below the tibial tuberosity, with a rate of reduction of 84.3% and 89.8%, respectively. Episodes of cellulitis were decreased from 1.9±0.3 to 0.6±0.1 times per year with statistical significance ($p<0.001$).

Discussion

Over the past eight years, the LVA operation rate has increased because of the development of the supermicrosurgery operative technology. Most lymphedema patients are associated with cancer and its effects. Due to the advancement of cancer treatment, the number of lymphedema patients and their life expectancy has been expanding. Based on our study, gynecologic malignancy, for example, cervical cancer and endometrial cancer, is the major cause of lower extremity lymphedema. This may be why lower extremity lymphedema affects females more[4,12].

The present study revealed that TAH with BSO was the most important risk factor among cancer-related surgical treatments, followed by inguinal lymph node dissection. Kunitake et al (2020) asserted that the significant risk factor of lymphedema was lymph node dissection. For adjuvant therapy, radiotherapy was regarded as an important risk factor[5,13,14]. The mechanism of lymphedema formation after surgery or radiation is the obstruction of lymphatic system due to inflammatory process and fibrosis at lymphedematous tissue[15].

In addition, obesity, which is defined as a BMI of 25 kg/m² or more, is considered a risk factor for lymphedema. Mehrara et al (2014) proposed a model of a vicious cycle in which there is a clear relationship between an increase in body weight and lymphatic dysfunction. Increasing body weight brings about lymphatic dysfunction, thereby leading to inflammation and the upregulation of the adipocytes differentiation gene, resulting in fibroadipose deposition and further impairment of the lymphatic function[8]. Other comorbidities are hypertension, diabetes mellitus, and dyslipidemia. However, there is no unambiguous evidence of an association between these comorbidities and lymphedema. It only showed that these occurrences are commonly found in this age group or obese patients. Such comorbidities may lead to a consideration of the most appropriate treatment, rather than being a direct effect of an operative outcome.

The present study's average duration, from the lymphedema onset to the first visit to the lymphedema clinic, was seven years. This is longer compared with the previous studies that reported that the mean duration was six and four years before visiting the clinic according to Koshima et al (2003) and Kristiansen et al (2020), respectively[16,17]. Lymphedema patients

Table 4. Circumferential reduction

	10 cm above patella	10 cm below tibial tuberosity	p-value
Pre-operative circumferential difference (cm); mean±SD	5.1±1.1	5.9±1.2	<0.0001
Circumferential reduction (cm); mean±SD	4.3±1.8	5.3±0.9	
Reduction rate (%)	84.3	89.8	

SD=standard deviation

Table 5. Episodes of cellulitis

	Episodes of cellulitis (times/year)			
	Pre-LVA; mean±SD	Post-LVA; mean±SD	p-value	Mean difference (95% CI)
Lower extremity (n=62)	1.9±0.3	0.6±0.1	<0.0001	−1.6 (−1.38 to −1.24)

LVA=lymphaticovenular anastomosis; SD=standard deviation; CI=confidence interval

in the present study were likely to suffer from this condition, rather than others, which was caused by an inadequate awareness of lymphedema, a low-quality system of providing for post-cancer-related surgical surveillance, or the patients' inaccessibility to medical advancements. Even though patients took time before visiting the clinic, according to Hara et al (2015), their LVA condition did not have a strong relationship to the duration-of-time factor, though it did depend on the patients' condition-predictors[18].

In terms of the lymphedema staging, various methods were based on the physical findings and patterns of lymphatic drainage in the imaging study. ISL and Campisi staging was commonly used as the clinical staging to assess the severity rate of lymphedema. Those staging methods classified patients based on skin changes, reversible edema, and skin infections[19,20]. The data collection revealed that two-thirds of the patients that underwent the LVA operation were in stage I-II of Campisi's staging. The present study found that the patients' lymphedema stage was earlier than the other studies in which the patients had at least irreversible edema[12,21]. The hypothetical reasons regarding why patients in an early stage of lymphedema underwent the LVA operation are cellulitis, failure of a conservative treatment, or a reduction in one's quality of life.

Although the surgical treatments for lymphedema are well-accomplished, other non-surgical treatments are basic. They consist of pressure garments, compression bandages, and manual lymphatic drainage, which reduce one's disturbing symptoms and slow the disease's progression. The concept behind these methods is to increase the interstitial pressure on the lymphedematous area by external compression. Thus, the excessive interstitial fluid returns to the central circulating system[20,22,23]. Because the operation for gynecologic malignancy is the important risk factor of lymphedema, the complex decongestive therapy combined with rehabilitation exercise is advised for early post-operative care to prevent lymphedema[24].

Apart from surgical treatments, skin care plays a significant role in non-surgical treatments. Lymphedema leads to various uncommon skin conditions such as soft-tissue swelling, skin fibrosis, skin crests, elephantiasis, or infections. According to the present study, patients did not take adequate care of their skincare and its relevant effects. Previous studies by Fife et al (2017) focused on how the lymphedematous-related inflammatory process and skin breakdown can lead to treatment failure resulting from improper pressure garments or applying of bandages, whereas the basic skincare methods, such as daily skin and nail hygiene, avoidance of trauma, skin moisturizer application, and dermatological preparations can maximize the treatment outcome[25].

Since the supermicrosurgery method has been widely introduced, studies have reported the success rate of the LVA operation in lymphedema treatment. These studies have indicated that adequate anastomosis was in the 2 to 12 range[11,18,26-28]. However, Koshima et al (2004) and Nagase et al (2005) reported that only two or three effective anastomoses could achieve an acceptable volume reduction[27,28]. The diameter of the lymphatic vessels and venules was also important. The diameter of the lymphatic vessels should be more than 0.5 to 0.7 mm for the lymphatic side and 0.7 to 1.0 mm for the venous side to provide sufficient flow[26,29].

Concerning the outcome measurements, studies have regarded the volumetric measurement as a gold standard for lymphedema assessment of the pre- and post-intervention[30,31]. However, in clinical practice, a circumferential reduction is more practical and approachable. This measurement has been found in studies, including that by Siriraj Hospital[16,18,21,26].

The LVA operation in the lower extremity has various successful outcomes. Koshima et al (2003) reported an average circumferential reduction of 4.7 cm, or 55.6% of preoperative excess[16]. Ito et al (2016) revealed that the reduction at 15 cm above the knee was 73.3%, at 15 cm below the knee was 45%, and the mean reduction rate was 63.8%[26]. Compared to the present study, the average circumferential reduction within eight months of the follow-up periods was 4.3 cm, or 84.3% of preoperative excess at 10 cm above the patella and 5.3 cm below the tibial tuberosity, or 89.8% of preoperative excess. The high success rate of the LVA operation in the present study is an achievement of LVA operations at Siriraj Hospital.

In terms of diameter reduction after the LVA operation, Chang et al (2015) reported that the LVA operation in upper extremities lymphedema had a better outcome, compared to the lower extremities' lymphedema[31]. According to the LVA data at Siriraj Hospital from Yodrabum et al (2021), the efficacy of LVA for the circumferential reduction of the upper extremity lymphedema was 0.9±0.6 cm or 15.5% of preoperative excess and 0.9±0.4 cm or 16.4% of preoperative excess for the position above and below the elbow, respectively[32]. However, in the

present study, the efficacy of the LVA operation for lymphedema in the lower extremity is greater than in the upper extremity. The present study results hypothesized that lymphedema in the lower extremities had a component of gravity-induced fluid leakage into the interstitial tissues caused by increased hydrostatic pressure. After bypass, the pathological lymphedematous tissues of the lower extremity were dramatically reduced.

A common complication of lymphedema is cellulitis. Almost one-third of lymphedema patients have experienced cellulitis, even in the early stage. The baseline incidence of cellulitis in lymphedema patients is 1.9 times per year. After the LVA operation, the cellulitis rate was reduced to 0.6 times per year, which is a statistically significant result. Compared with the study by Mihara et al (2014), they reported that cellulitis rate was decreased from 1.46 times per year to 0.18 times per year. The Mihara et al's study was in line with that of Qiu et al (2020), in which the cellulitis rate was reduced from 1.4 times per year to 0.6 times per year. Thus, previous studies confirm that LVA contributes to cellulitis depletion, with statistical significance[12,33].

Operative management of lymphedema can be categorized into two groups, which are ablative procedures and physiological mimicking procedures. The ablative procedures, or reductive surgery, can dramatically reduce excess skin and subcutaneous tissue. However, they cannot permanently reduce those lymphedematous volume. Instead of that, physiological mimicking procedures such as LVA or vascularized lymph node transfer (VLNT) can reproduce the lymphatic drainage tract, which are significant for long term outcomes[34].

Other complications associated with lymphedema are the impacts on physical or psychological wellness. On the one hand, physical disturbance can include discomfort, heaviness, pain, recurrent infection, or even permanent disability. Additionally, patients can experience anxiety, depression, embarrassment, and stress due to their limb disfigurement[31,35]. Accordingly, public health organizations should develop an effective lymphedema healthcare system that includes specialized clinics composed of a multidisciplinary team to help patients deal with these problems.

The limitation in the present study was the short follow-up periods in some patients. It might not show the highly effectiveness of LVA operation on circumferential reduction. In addition, the cellulitis rate is lower than the exact rate.

Conclusion

LVA can be regarded as an effective operation for lower extremity lymphedema. The affected limb circumference is significantly reduced after the operation. Likewise, in the case of cellulitis episodes, LVA can satisfactorily alleviate the rate of infection, which results in improving these patients' quality of life. In addition to the previous studies that have emphasized that LVA can reduce the limb circumference in the upper extremity more than in the lower extremity, the present study demonstrated that performing the LVA operation in the lower extremity also had a significant outcome.

It should be noted that patients' education in non-surgical treatments is also essential. Different kind of such treatments can be synergized to maximize the operative treatment outcomes and to slow the progress of the disease.

What is already known about this topic?

LVA is a successful surgical operation for lymphedema. It can significantly reduce the limb circumference and episodes of cellulitis. However, the previous studies suggested that the outcome of LVA in the upper extremity lymphedema is better than for lower extremity lymphedema.

What this study adds?

The LVA operation for lower extremity lymphedema can achieve a satisfactory outcome, with a slightly higher benefit than the LVA operation in the upper extremity. Regarding this key finding, this study hypothesis is that lower extremity lymphedema has more components of fluid-rich tissues than the upper extremity lymphedema, which is composed of fibroadipose tissues. Consequently, lower extremity lymphedema patients should be encouraged to undergo the LVA operation.

Conflicts of interest

The authors declare no conflict of interest.

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