SVEUČILIŠTE U SPLITU

MEDICINSKI FAKULTET

IVANA KLARIĆ - KUKUZ

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Doktorski rad

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„Little by little, one travels far.“
J. R. R. Tolkien

Na kraju, hvala svima koji su bili dio ovog puta, vidljivo ili nevidljivo, glasno ili tiho. Svaki vaš trag utkan je u ovaj rad!

SADRŽAJ

POPIS OZNAKA I KRATICA

BCRL – limfedem povezan s rakom dojke

BIS – bolnički informacijski sustav

BMI – indeks tjelesne mase

CI – interval pouzdanosti

COSMIN – standardi temeljeni na konsenzusu za odabir mjernih instrumenata u zdravstvu

EQ-5D – EuroQol upitnik s 5 dimenzija

HRQoL – kvaliteta života povezana sa zdravljem

ICC – intraklasni koeficijent korelacije

OR – omjer izgleda

ICF – Međunarodna klasifikacija funkcioniranja, onesposobljenosti i zdravlja

IQR – interkvartilni raspon

ISL – Međunarodno društvo za limfologiju

KMO – Kaiser-Meyer-Olkin mjera adekvatnosti uzorka

LE – limfedem

LYMQoL-Arm – upitnik kvalitete života osoba s limfedemom ruke

LYMQoL-UL-CRO – hrvatska verzija upitnika LYMQoL za gornji ekstremitet

MCS – mentalna komponenta kvalitete života

MKF – Međunarodna klasifikacija funkcioniranja, onesposobljenosti i zdravlja

PCS – tjelesna komponenta kvalitete života

PINRS – numerička ljestvica intenziteta boli

PROM – mjere ishoda koje prijavljuju pacijenti

RVC – relativna promjena volumena

SBS – subakromijalni bolni sindrom

SD – standardna devijacija

SEM – standardna pogreška mjerenja

SF-36 – kratki zdravstveni upitnik s 36 čestica

ULD – disfunkcija gornjeg ekstremiteta

PREGLED OBJEDINJENIH RADOVA

1. Klarić-Kukuz I, Aljinović J, Barun B, Roki M, Benzon B, Budimir Mršić D, Marinović-Guić M, Poljičanin A. Subacromial pain syndrome in breast cancer survivors-are structural shoulder changes verified by ultrasound clinically relevant? *Diagnostics (Basel)***.** 2025;15(1):70. doi:10.3390/diagnostics15010070.
2. Klarić-Kukuz I, Mršić DB, Matana A, Barun B, Aljinović J, Marinović-Guić M, Poljičanin A. High-frequency ultrasonography imaging: anatomical measuring site as potential clinical marker for early identification of breast cancer-related lymphedema. *Biomedicines***.** 2025;13(6):1396. doi:10.3390/biomedicines13061396
3. Klarić-Kukuz I, Ćurković A, Grančić J, Aljinović J, Barun B, Pivalica D, Poljičanin A. Measuring what matters for breast cancer survivors: translation, cross-cultural adaptation and validation of the Croatian version of Lymphedema Quality of Life Tool-Arm. *J Clin Med. 2026;15(2):465.* Doi:10.3390/jcm15020465.

1. UVOD

Rak dojke predstavlja najčešće dijagnosticiranu zloćudnu bolest u žena širom svijeta. U 2022. godini zabilježeno je približno 2,3 milijuna novih slučajeva u svijetu, što čini oko 25 % svih zloćudnih bolesti u žena (1). Sličan obrazac učestalosti bilježi se i u Hrvatskoj, gdje je rak dojke također najčešći zloćudni tumor u žena. Prema najnovijim podacima, u 2023. godini dijagnosticirana su 3 293 nova slučaja, što čini oko 26 % svih novootkrivenih slučajeva raka u žena u Hrvatskoj (2).

Epidemiološki trendovi ukazuju na daljnji porast broja novodijagnosticiranih slučajeva, uz procjenu da bi godišnji broj novih slučajeva u svijetu mogao dosegnuti 3,55 milijuna do 2050. godine ako trenutni epidemiološki obrasci ostanu nepromijenjeni. Iako apsolutni broj oboljelih i umrlih od raka dojke na svjetskoj razini raste, u mnogim visoko razvijenim zemljama svijeta bilježi se pad stope smrtnosti, što se pripisuje promjenama u čimbenicima rizika, kvalitetnijoj registraciji zloćudnih bolesti te napretku u metodama ranog otkrivanja i liječenja bolesti (1, 3, 4).

Ova bolest ima složenu etiologiju, pri čemu je starija životna dob najznačajniji pojedinačni čimbenik rizika, uz genetsku predispoziciju te reproduktivne i hormonske čimbenike. Osobe starije od 50 godina čine oko 80 % bolesnica s rakom dojke. Ishodi liječenja i preživljenje uvelike ovise o stadiju bolesti u trenutku postavljanja dijagnoze, kao i o molekularnom podtipu raka, pri čemu je rano otkrivanje ključan prognostički čimbenik (5, 6).

Liječenje raka dojke temelji se na multidisciplinarnom pristupu te obuhvaća kirurške, sustavne i potporne terapijske pristupe (7). Napredak u dijagnostičkim metodama i razvoju manje invazivnih, ciljano usmjerenih i bioloških terapija značajno je poboljšao ishode liječenja (8). Zahvaljujući napretku u dijagnosticiranju i liječenju raka dojke u visokorazvijenim zemljama, stopa petogodišnjeg preživljenja iznosi oko 90 % (4).

Unatoč uspješno provedenom liječenju, velik broj osoba liječenih od raka dojke suočava se s različitim dugotrajnim posljedicama koje nadilaze samu kontrolu osnovne bolesti. Dostupna literatura navodi kako gotovo 90 % žena ima kratkoročne funkcionalne poteškoće šest mjeseci nakon liječenja, dok njih 62 % prijavljuju dugoročne poteškoće i šest godina nakon završetka liječenja (11). Ove poteškoće uključuju kronični umor, limfedem, bol te funkcionalne, psihološke i socijalne poteškoće koje u konačnici dovode do smanjene kvalitete života (9, 10).

S obzirom na dugotrajnost i heterogenost navedenih posljedica, koncept preživljenja nakon raka dojke nadilazi završetak početnog onkološkog liječenja te obuhvaća različite faze liječenja i života s promjenjivim zdravstvenim potrebama. U tom kontekstu, prema izvješću „Od pacijenata s rakom do preživjele osobe: Izgubljeni u prijelazu" *(engl. From Cancer Patient to Cancer Survivor: Lost in Transition)*, razdoblje preživljenja nakon raka dojke dijeli se u tri faze: akutnu, produljenu i trajnu fazu.

Akutna faza obuhvaća razdoblje od postavljanja dijagnoze i početnog liječenja. Produljena faza obuhvaća razdoblje nakon završetka liječenja tijekom kojeg se provodi učestali nadzor radi otkrivanja povrata bolesti. Trajna ili dugotrajna faza započinje pet godina nakon primarnog liječenja raka dojke, kada se rizik od povrata bolesti smanjuje, ali tjelesne, psihološke i socijalne posljedice raka i dalje mogu biti prisutne (11-13). U dugotrajnoj fazi zdravstvena skrb više nije usmjerena isključivo na onkološki ishod, nego na rano prepoznavanje, procjenu i sustavno praćenje posljedica bolesti i liječenja, osobito onih koje utječu na funkcionalnu sposobnost, sudjelovanje u svakodnevnim aktivnostima i kvalitetu života liječenih osoba (14-16).

Slijedom navedenoga, suvremena literatura sve više prepoznaje dugotrajno preživljenje nakon raka dojke kao zasebnu fazu zdravstvene skrbi koja zahtjeva specifično planirane, dugoročne i individualizirane intervencije, a ne samo povremeno praćenje nakon završetka onkološkog liječenja (14, 16-18).

Rehabilitacija, u skladu s Međunarodnom klasifikacijom funkcioniranja, onesposobljenosti i zdravlja (MKF) *(engl. International Classification of Functioning, Disability and Health - ICF)* ima ključnu ulogu u dijagnosticiranju i liječenju tjelesnih, psiholoških i socijalnih posljedica bolesti te bi trebala biti integrirana u sve faze onkološke skrbi, uključujući i dugoročno razdoblje nakon završetka liječenja raka dojke (14, 19, 20). Unatoč tome, postojeće smjernice za skrb o preživjelima od raka dojke uglavnom su općenite te se primarno usmjeravaju na praćenje recidiva, sekundarne prevencije i upravljanje nuspojavama sistemskog liječenja, dok su mišićno-koštane i limfne komplikacije često marginalno zastupljene ili obrađene bez jasnih preporuka za procjenu, praćenje i liječenje (17, 18). Posljedica toga je neintegrirana zdravstvena skrb u kojoj su rehabilitacija i fizikalna terapija često nedovoljno dostupne, zakašnjele ili ovise o individualnoj inicijativi pacijenta i pojedinih zdravstvenih djelatnika (16, 19). Također nedostaje jasno definiran

i detaljno razrađen standard zdravstvene skrbi specifičan za osobe koje su preživjele rak dojke (14, 16-18).

Brojna istraživanja ukazuju na to da su neliječene ili nedovoljno prepoznate komplikacije mišićno-koštanog i limfnog sustava gornjeg ekstremiteta vrlo česte u populaciji žena liječenih od raka dojke te zahvaćaju značajan udio žena tijekom dugotrajnog razdoblja preživljenja. Procjenjuje se da ograničenje pokretljivosti ramenog obruča pogađa približno polovicu liječenih žena, smanjenje mišićne snage oko četvrtinu, dok se limfedem razvija u više od petine žena liječenih od raka dojke (21, 22). Ove komplikacije rijetko se javljaju izolirano, već su često prisutne u različitim kombinacijama, pri čemu se međusobno isprepleću i pojačavaju, stvarajući kompleksan klinički obrazac obilježen kroničnom boli, smanjenom pokretljivošću, poremećenom funkcijom i progresivnom funkcionalnom onesposobljenošću ako se ne prepoznaju i ne liječe pravodobno (14, 15, 23).

Funkcionalne posljedice koje se javljaju nakon liječenja raka dojke u literaturi se često opisuju pojmom disfunkcije gornjeg ekstremiteta *(engl. upper limb dysfunction, ULD),* koji obuhvaća različite poremećaje funkcije ruke i ramenog obruča, uključujući smanjeni opseg pokreta, slabost mišića, bol, osjetne promjene i limfedem. Navedene promjene mogu otežati korištenje zahvaćenog ekstremiteta u svakodnevnim aktivnostima, radnim zadacima i društvenom sudjelovanju (24, 25). Među njima se posebno ističe limfedem koji, osim vidljivih morfoloških promjena, često prati osjećaj težine, nelagode i nesigurnosti pri korištenju zahvaćenog ekstremiteta, što može dovesti do smanjene spontanosti pokreta i izbjegavanja izvođenja određenih aktivnosti (26).

Stoga, rano prepoznavanje i sustavno praćenje poremećaja mišićno-koštanog i limfnog sustava, uz pravodobnu primjenu ciljanih intervencija usmjerenih na očuvanje funkcije, predstavljaju ključne elemente dugoročne skrbi za žene liječene od raka dojke (11, 27). Posebnu kliničku važnost imaju komplikacije poput boli i ograničenja pokreta ramenog obruča, subakromijalnog bolnog sindroma te limfedema gornjeg ekstremiteta, koje mogu značajno narušiti funkcionalnu sposobnost, sudjelovanje u svakodnevnim aktivnostima i kvalitetu života.

Unatoč rastućem broju žena u dugotrajnoj fazi preživljenja, još uvijek ne postoje jasno definirane i standardizirane smjernice za sustavno praćenje, rano otkrivanje i integrirano

rehabilitacijsko zbrinjavanje ovih komplikacija. Posljedično, postoji potreba za dodatnim istraživanjima koja će doprinijeti boljem razumijevanju njihove pojavnosti, međusobne povezanosti te utjecaja na funkcionalnu sposobnost i kvalitetu života u dugoročnom razdoblju nakon liječenja.

Polazeći od navedenih kliničkih i znanstvenih izazova, ova disertacija je usmjerena na istraživanje subakromijalnog bolnog sindroma (SBS) i limfedema (LE) gornjeg ekstremiteta kao funkcionalno najznačajnijih i međusobno povezanih komplikacija u dugotrajnoj fazi preživljenja nakon raka dojke. U tom kontekstu, cilj rada jest doprinijeti boljem razumijevanju kliničkih, ultrazvučnih i funkcionalnih obilježja navedenih stanja te njihove povezanosti sa subjektivnim doživljajem simptoma i kvalitetom života žena nakon liječenja raka dojke.

U nastavku su prikazana tri znanstvena članka koji, svaki iz svoje istraživačke perspektive, analiziraju navedene aspekte i zajedno čine znanstvenu osnovu ove disertacije.

1.1. Povezanost subakromijalnog bolnog sindroma i liječenja raka dojke

Subakromijalni bolni sindrom (SBS) *(engl. subacromial pain syndrome)* jedan je od najčešćih uzroka boli u području ramena te predstavlja značajan klinički problem u području mišićno-koštanih poremećaja. Pojam se koristi za opis skupine stanja koja zahvaćaju strukture subakromijalnog prostora i dovode do boli i funkcionalnog ograničenja ramena (28, 29). U literaturi se često koristi i naziv sindrom sraza ramena *(engl. impingement syndrome),* no njegova se primjena u novije vrijeme kritizira zbog nedovoljne specifičnosti i činjenice da obuhvaća različite patoanatomske i funkcionalne mehanizme koji mogu dovesti do slične kliničke slike zbog čega se sve češće preporučuje uporaba termina subakromijalni bolni sindrom (30, 31).

Subakromijalni bolni sindrom smatra se multifaktorijalnim poremećajem, pri čemu nastanak simptoma može biti povezan s različitim anatomsko-funkcionalnim promjenama (31). U literaturi se navode čimbenici poput upalnih i degenerativnih promjena tetiva i subakromijalne burze, slabosti ili disfunkcije muskulature rotatorne manšete i stabilizatora lopatice, skraćenosti stražnje kapsule glenohumeralnog zgloba te koštanih i mekotkivnih promjena koje mogu dovesti do smanjenja subakromijalnog prostora (28, 32). Prema zahvaćenim strukturama razlikuju se subakromijalni, unutarnji i subkorakoidni sindrom sraza ramena (29).

U kontekstu raka dojke nastanak SBS-a poprima dodatnu kliničku važnost jer su žene koje su preživjele rak dojke izložene specifičnim rizicima povezanim s liječenjem. Iako navedene terapijske metode same po sebi ne moraju uzrokovati primarno strukturno oštećenje ramenog zgloba, funkcionalne promjene u kinetici i skapulotorakalnoj koordinaciji mogu posljedično dovesti do klinički značajne boli i disfunkcije (32-35). Brojni čimbenici povezani s liječenjem, poput kirurškog zahvata na dojci i disekcije pazuha, radioterapije, postoperativnog limfedema te posljedične poštede i promjene posture i mehanike pokreta, dovode žene koje su preživjele rak dojke u povećan rizik od razvoja SBS-a (36). Prethodno je dokazana visoka učestalost strukturnih oštećenja ramena u ovoj populaciji, poput rupture tetive supraspinatusa (53.3 %), tenosinovitis tetive bicepsa (13.3 %) te subdeltoidnog burzitisa (13.3 %). Navedena strukturna oštećenja mogu se pouzdano detektirati ultrazvučnom dijagnostikom (28, 37). Međutim, ove tegobe nerijetko ostaju neprepoznate ili se pogrešno smatraju dijelom očekivanog oporavka, zbog čega simptomi mogu biti dugotrajni i prijeći u kroničnu bol (9, 38).

Iako se u znanstvenoj literaturi sve češće naglašava moguća uzročno-posljedična veza između liječenja raka dojke, boli u ramenu i SBS-a, slikovne studije koje se bave tom temom rijetke su, a njihovi nalazi često su neuvjerljivi (28, 37, 39-41). Dosad nije pouzdano utvrđena učestalost simptomatskih i asimptomatskih oštećenja rotatorne manšete u populaciji žena liječenih od raka dojke, što predstavlja značajan istraživački nedostatak. Nadalje, većina studija provedenih u ovoj populaciji uključuje male uzorke, heterogene metodologije i različite dijagnostičke pristupe, što otežava donošenje čvrstih zaključaka i ukazuje na potrebu za standardiziranim i metodološki opsežnijim istraživanjima (41-43).

1.2. Promjene na limfnom sustavu nakon liječenja raka dojke

Sekundarni limfedem povezan s liječenjem raka dojke *(engl. Breast cancer related lymphoedema, BCRL)* predstavlja kronično, progresivno nakupljanje limfne tekućine u međustaničnom tkivu. Nastaje kao posljedica kirurških zahvata, disekcije aksilarnih limfnih čvorova ili radioterapije. Posljedično dolazi do zastoja međustanične tekućine, njezina nakupljanja u zahvaćenom području te strukturnih i funkcionalnih promjena kože i potkožnog tkiva zahvaćenog limfedemom (44-46).

Pojavnost BCRL-a iznosi približno 21 %, no teško ju je precizno odrediti zbog heterogenosti dijagnostičkih metoda, terapijskih pristupa i individualnih karakteristika pacijentica (47, 48). Limfedem predstavlja trajni rizik za sve osobe koje su preživjele rak dojke te je povezan s brojnim kliničkim, psihološkim i socijalnim posljedicama. Najčešći simptomi uključuju oteklinu, bol, osjećaj nelagode, zategnutosti i težine, kao i funkcionalne poteškoće (25-28). Ove tegobe ne utječu samo na fizičku izvedbu svakodnevnih aktivnosti nego značajno narušavaju tjelesnu sliku, mentalno zdravlje i sudjelovanje u društvenim aktivnostima, pridonoseći smanjenju kvalitete života (49, 50). Osim toga, BCRL predstavlja i značajno financijsko opterećenje za pacijentice, njihove skrbnike i zdravstveni sustav.

Dodatni je problem što se limfedem najčešće dijagnosticira tek u trenutku kada postane vidljiv, odnosno kada se razvije klinički prepoznatljiva, izražena oteklina zahvaćenog dijela tijela (22, 26, 49, 52). Zbog toga aktualni modeli praćenja naglašavaju potrebu za sustavnim i dugotrajnim praćenjem rizičnih pacijentica od trenutka postavljanja dijagnoze raka dojke kako bi se omogućilo što ranije prepoznavanje početnih promjena i sprječavanje progresije limfedema (23, 26, 27, 49, 53).

Iako se u kliničkoj praksi najčešće koriste mjerenja volumena i opsega gornjih ekstremiteta te procjena prisutnost i simptoma, ove metode često nisu dovoljno osjetljive ni pouzdane za otkrivanje ranog subkliničkog stadija BCRL-a (54-57). S druge strane, preciznije tehnike poput magnetske rezonancije, limfoscintigrafije te fluorescentne limfografije uz pomoć indocijaninske zelene boje, iako informativne, često su skupe, logistički zahtjevne i invazivne (49, 58, 59).

Ultrazvučna dijagnostika BCRL-a nameće se kao obećavajuće, neinvazivno i dostupno sredstvo za objektivnu procjenu promjena u koži i potkožju, koja se u te svrhe tek nedavno počela sustavno istraživati (58, 60, 61). Većina ranije provedenih studija uglavnom je bila usmjerena na obilježja uznapredovalih stadija limfedema (61-66). Ultrazvučne studije koje opisuju subklinički limfedem rijetke su (64). Ultrazvučnim prikazom moguće je razlikovati različite obrasce progresije limfedema identifikacijom promjena ehogenosti i anehogenosti tkiva, čime se dobiva vrijedan uvid u prisutnost edema te fibroze kože i potkožja nastalih kao posljedica kronične prirode bolesti (65, 67-69). Takav pristup dijagnostici mogao bi omogućiti raniju intervenciju, spriječiti daljnju progresiju bolesti i stvoriti preduvjete za bolju kvalitetu života oboljelih osoba (27, 70–72).

1.3. Kvaliteta života oboljelih od limfedema gornjeg ekstremiteta povezanog s liječenjem raka dojke

S obzirom na to da liječenje raka dojke može dovesti do brojnih posljedica koje zahvaćaju gornji ekstremitet, uključujući limfedem, subakromijalni bolni sindrom, oštećenja ramenih struktura, smanjen opseg pokreta i kroničnu bol, procjena kvalitete života postala je ključna komponenta razumijevanja ukupnog tereta bolesti u ovoj populaciji. Limfedem i poremećaji ramena često se javljaju istodobno, međusobno se isprepliću te pridonose značajnim funkcionalnim ograničenjima, smanjenoj samostalnosti u svakodnevnim aktivnostima i narušenoj tjelesnoj slici.

Upravo zato procjena utjecaja BCRL-a na svakodnevni život osoba liječenih od raka dojke zahtijeva pristup koji nadilazi objektivne kliničke mjere te uključuje i subjektivno iskustvo bolesti (73). Budući da limfedem zahvaća tjelesne, funkcionalne, emocionalne i socijalne vidove života, u tu se svrhu sve češće koriste upitnici temeljeni na iskazima pacijentica *(engl. patient-reported outcome measures, PROMs)*, koji omogućuju uvid u percepciju simptoma, psihološki teret bolesti i njezin utjecaj na kvalitetu života povezanu sa zdravljem *(engl. Health related Quolity of Life, HRQoL)* (73-75).

Iako se u kliničkoj praksi mogu koristiti generički upitnici kvalitete života, poput Upitnika o zdravstvenom statusu Kratka forma s 36 čestica *(engl. Short Form 36 Health Survey, SF-36)* ili EuroQol 5 dimenzija *(engl. EuroQol 5 Dimensions, EQ-5D)*, oni ne uspijevaju obuhvatiti specifične izazove povezane s limfedemom, uključujući funkcionalna ograničenja, promjene tjelesne slike, negativan emocionalan doživljaj bolesti, strah od pogoršanja simptoma te ograničenja u društvenom sudjelovanju (74, 75). Zbog toga, su razvijeni specifični instrumenti namijenjeni procjeni limfedema koji preciznije mjere subjektivan teret simptoma i njihov utjecaj na različite domene funkcioniranja (76, 77).

Najčešće korišten alat za specifičnu procjenu kvalitete života žena s limfedemom ruke jest upitnik Kvaliteta života oboljelih od limfedema - ruka, *(engl. Lymphedema Quality of Life Questionnarie-Arm, LYMQoL-Arm)* (78). Upitnik je izvorno razvijen na engleskom jeziku, a zatim kulturološki prilagođen i validiran u više zemalja, uključujući Italiju, Švedsku, Tursku, Ujedinjeno

Kraljevstvo, Koreju, Kinu i Nizozemsku. U svim ovim populacijama upitnik je pokazao snažna psihometrijska svojstva te se dokazao korisnim u kliničkoj praksi i istraživanjima (78-84). LYMQoL omogućuje detaljnu procjenu samoprocijenjenih ishoda u domenama izgleda, funkcije, simptoma i raspoloženja, pri čemu pomaže u planiranju personaliziranih intervencija i poboljšanju kvalitete života povezane sa zdravljem (HRQoL) žena s BCRL-om (85). Ipak, postoje nalazi koji upućuju na to da rezultati upitnika LYMQoL ne koreliraju uvijek s objektivnim mjerama poput volumena ekstremiteta, što otvara pitanje konstrukcijske valjanosti i upućuje na složen odnos između subjektivnog i objektivnog iskustva bolesti (78, 86).

Ovaj instrument omogućuje detaljnu procjenu samoprijavljenih ishoda u domenama izgleda, funkcije, simptoma i raspoloženja, čime pruža sveobuhvatan i višedimenzionalan uvid u stanje pacijentica koje žive s limfedemom. Takav pristup osobito je vrijedan jer podupire planiranje personaliziranih intervencija te omogućuje praćenje promjena tijekom rehabilitacije i evaluaciju učinaka terapije (23, 49, 85).

Unatoč širokoj međunarodnoj primjeni i dokazanoj koristi upitnika LYMQoL u različitim kulturnim i kliničkim okruženjima, u Hrvatskoj do sada nije postojala validirana verzija ovog instrumenta za žene s BCRL-om. Nedostatak standardiziranog i kulturološki prilagođenog alata značio je da se procjena kvalitete života u ovoj populaciji oslanjala na generičke upitnike ili instrumente koji nisu bili formalno validirani u hrvatskom jeziku i zdravstvenom sustavu. Time je postojala mogućnost smanjene osjetljivosti na specifične probleme s kojima se susreću žene liječene od raka dojke, uključujući razlike u zdravstvenim praksama, kulturnoj percepciji tijela, emocionalnom doživljavanju bolesti i društvenim ulogama.

Validacijom ovog instrumenta zdravstvenim djelatnicima omogućuje se preciznija, pacijenticama relevantnija i metodološki utemeljena procjena subjektivnog tereta limfedema, što u konačnici pridonosi kvalitetnijem planiranju liječenja i poboljšanju ukupnih ishoda rehabilitacije žena s BCRL-om.

Uzimajući u obzir složenost mišićno-koštanih i limfnih komplikacija nakon liječenja raka dojke te njihov značajan utjecaj na funkcionalnu sposobnost i kvalitetu života, nameće se potreba za integriranim istraživačkim pristupom koji istodobno obuhvaća kliničke, slikovne i funkcionalne pokazatelje bolesti. U tom kontekstu, ova disertacija je usmjerena na istraživanje subakromijalnog

bolnog sindroma i limfedema gornjeg ekstremiteta te na procjenu njihove povezanosti s kvalitetom života žena liječenih od raka dojke, s ciljem unaprjeđenja ranog prepoznavanja komplikacija i razvoja učinkovitijih rehabilitacijskih pristupa u hrvatskom zdravstvenom kontekstu.

2. CILJEVI I HIPOTEZE ISTRAŽIVANJA

2.1. Ciljevi istraživanja

Glavni cilj:

Procijeniti vrijednost ultrazvučnih mjerenja u otkrivanju strukturnih mišićno-koštanih promjena i ranih oblika limfedema te validirati standardizirani instrument za procjenu kvalitete

života s ciljem poboljšanja dijagnostičkih i rehabilitacijskih postupaka u skrbi za žene liječene od raka dojke.

Specifični ciljevi:

1. Utvrditi učestalost i vrstu ultrazvučno potvrđenih strukturnih promjena u području ramena u populaciji žena liječenih od raka dojke te ispitati njihovu povezanost s pojavom boli.
2. Procijeniti dijagnostičku vrijednost ultrazvučnih mjerenja debljine kože i potkožnog tkiva za rano prepoznavanje limfedema u usporedbi s konvencionalnim metodama procjene volumena.
3. Prevesti, kulturološki prilagoditi i psihometrijski validirati hrvatsku verziju upitnika LYMQoL-Arm za procjenu kvalitete života žena s limfedemom gornjeg ekstremiteta.
4. Ispitati povezanost minimalnih volumnih promjena gornjeg ekstremiteta s dimenzijama kvalitete života izmjerenima upitnikom Lymphedema Quality of Life Questionnaire-Upper Limb- Croatian (LYMQoL-UL-CRO).

2.2. Hipoteze

Hipoteza 1

Ultrazvučnom analizom moguće je pouzdano detektirati strukturne promjene u području ramena kod žena liječenih od raka dojke, pri čemu će prisutnost patoloških nalaza biti povezana s pojavom boli u ramenu.

Hipoteza 2

Ultrazvučna mjerenja debljine kože i potkožnog tkiva omogućuju rano prepoznavanje limfedema te mogu detektirati tkivne promjene i u fazi minimalnih volumnih promjena koje nisu nužno prepoznate konvencionalnim metodama procjene.

Hipoteza 3

Hrvatska verzija upitnika LYMQoL-Arm (LYMQoL-UL-CRO) valjan je i pouzdan mjerni instrument za procjenu kvalitete života žena s limfedemom gornjeg ekstremiteta.

Hipoteza 4

Upitnik LYMQoL-UL-CRO osjetljiv je za otkrivanje minimalnih volumnih promjena gornjeg ekstremiteta te može razlikovati žene s ranim (minimalnim) volumenskim povećanjem od žena bez klinički značajnih promjena.

3. PREGLED METODOLOGIJE OBJEDINJENIH RADOVA

3.1. Klinički i sociodemografski podaci ispitanica

U sva tri prospektivna opažajna istraživanja sudjelovale su ukupno 84 ispitanice liječene od raka dojke. Ispitanice su bile uključene u program praćenja i rehabilitacije u Dnevnoj bolnici za limfedem pri Zavodu za fizikalnu medicinu i rehabilitaciju s reumatologijom Kliničkog bolničkog centra Split.

Prikupljanje podataka provedeno je u razdoblju od studenoga 2023. do travnja 2024. godine. Sva mjerenja provedena su na Zavodu za fizikalnu medicinu i rehabilitaciju s reumatologijom te na Kliničkom zavodu za dijagnostičku i intervencijsku radiologiju Kliničkog bolničkog centra Split.

Podaci o povijesti bolesti prikupljeni su iz bolničkog informacijskog sustava (BIS) uz pomoć strukturiranog upitnika. Sociodemografski podaci prikupljeni su od ispitanica tijekom provođenja ostalih mjerenja putem strukturiranog upitnika.

3.2. Klinička procjena limfedema

U sva tri istraživanja provedena je klinička procjena limfedema svih ispitanica, temeljena na klasifikaciji Međunarodnog društva za limfologiju (engl. International Society of Lymphology - ISL), od strane liječnika specijalista fizikalne medicine i rehabilitacije s višegodišnjim iskustvom rada s pacijentima oboljelima od limfedema (87). Limfedem se na ovaj način opisuje kroz četiri stadija (0-III). Stadij 0 označava stanje u kojem postoji oštećenje ili opstrukcija limfnog sustava, ali bez klinički vidljive otekline. Iako volumen ekstremiteta ostaje normalan, mogu biti prisutne rane promjene tkiva, kao i subjektivni simptomi poput osjećaja težine, napetosti, nelagode ili parestezije. Ovaj stadij može trajati mjesecima ili godinama prije pojave vidljivog edema. Stadij I karakterizira reverzibilno nakupljanje međustanične tekućine. Oteklina je obično mekana te se smanjuje ili u potpunosti povlači elevacijom ekstremiteta. U ovom stadiju još nema značajnih strukturnih promjena tkiva. Stadij II obilježen je nepovratnim promjenama. Oteklina se više ne povlači u potpunosti elevacijom ekstremiteta. U ranoj fazi stadija II edem može biti donekle mekan i udubljiv, dok u kasnijoj fazi postaje neudubljiv zbog fibroze i masnih infiltracija. Prisutne su izraženije strukturne promjene kože i potkožnog tkiva. Stadij III predstavlja najozbiljniji oblik

limfedema, karakteriziran izraženim povećanjem volumena ekstremiteta, fibroznim i masnim promjenama te trofičkim promjenama kože, uključujući hiperkeratozu, akantozu, papilomatozu i kožne nabore. Često su prisutne ponavljajuće infekcije i značajno funkcionalno oštećenje (66, 87, 88).

Procjena limfedema na temelju razlike u opsegu gornjeg ekstremiteta, korištena kao dijagnostički kriterij u prvom vlastitom istraživanju, provedena je kod svih ispitanica od strane doktorandice, magistre fizioterapije s edukacijom i višegodišnjim iskustvom u radu s pacijenticama oboljelima od limfedema. Dodatno je kod 20 % nasumično odabranih pacijentica mjerenje proveo drugi educirani magistar fizioterapije kako bi se omogućila procjena pouzdanosti mjerenja. Najprije je procijenjena pouzdanost mjerenja opsega ekstremiteta za svakog ispitivača zasebno *(engl. intra-observer reliability),* a zatim i međuispitivačka pouzdanost usporedbom rezultata između ispitivača *(engl. inter-observer reliability).* Postupak je detaljno opisan u izvornom istraživanju (89).

U ovoj studiji korišteni su prethodno opisani protokoli za mjerenje cirkumferencije gornjih ekstremiteta. Mjerenja su provedena u sjedećem položaju ispitanice, s rukom oslonjenom na podesivi hidraulični stol, s ramenom u fleksiji od približno 90° i podlakticom u pronaciji na podlozi stola u opuštenom položaju (54). Mjerenja su provedena na unaprijed definiranih pet mjernih točaka na oba gornja ekstremiteta u razmacima od 10 cm. Početna mjerna točka bila je anatomska referenca, stiloidni nastavak lakatne kosti (označen kao točka 0). Opseg je mjeren na svakoj točki uz pomoć uske fleksibilne mjerne trake „Juzo“ s preciznošću od 1 mm. Na svakoj mjernoj točki mjerenja su ponovljena tri puta, a srednje vrijednosti zabilježene su na standardiziranom obrascu (10, 54). U ovom istraživanju limfedem je definiran primjenom najčešće korištenog objektivnog kliničkog dijagnostičkog kriterija, prema kojem se limfedem smatra prisutnim kada je razlika u opsegu između gornjih ekstremiteta ≥ 2 cm, izmjerena na bilo kojoj pojedinoj mjernoj točki duž gornjeg ekstremiteta (54, 90). Procjena limfedema na temelju razlike u volumenu gornjih ekstremiteta izračunata je primjenom formule krnjeg stošca, koristeći mjere opsega za četiri segmentna volumena (0-10 cm, 10-20 cm, 20-30 cm i 30-40 cm), kako je opisano u literaturi (57). Omjer volumena ekstremiteta izražen je kao relativna promjena volumena *(engl. relative volume change, RVC)* između zahvaćenog i nezahvaćenog ekstremiteta, normalizirana prema volumenu kontralateralnog ekstremiteta (91, 92). Klinička definicija limfedema postavljena je pri vrijednosti

RVC ≥ 10 %, što predstavlja uobičajeni dijagnostički prag za potvrdu limfedema, dok se vrijednosti ispod tog praga ne mogu koristiti za njegovo isključivanje (93). Međutim, budući da je primarni cilj naših istraživanja bio rano otkrivanje limfedema povezanog s rakom dojke, kao i utjecaj minimalnih razlika u volumenu na kvalitetu života žena liječenih od raka dojke, dijagnostički kriteriji prilagođeni su primjeni nižeg volumenskog praga (RVC ≥ 5 %), koji omogućuje otkrivanje minimalnih volumenskih promjena prije razvoja klinički izraženog limfedema (46, 49, 50, 59). Detaljan opis postupka definiranja limfedema objavljen je u izvornim istraživanjima (89, 94).

3.3. Ultrazvučna procjena struktura ramena

Ultrazvučna procjena mišićno-koštanog sustava za potrebe prvog istraživanja provedena je od strane dvaju liječnika specijalista fizikalne medicine i rehabilitacije s višegodišnjim iskustvom u izvođenju mišićno-koštane ultrazvučne dijagnostike. Mjerenja su provedena uz pomoć linearne ultrazvučne sonde (12 MHz) na uređaju GE Health Care Versana Premier V2 (Chicago, Illinois, SAD), prema standardiziranom protokolu (95). Podaci potrebni za izračun pouzdanosti mjerenja prikupljeni su istoga dana kao i osnovna mjerenja, a mjerenja su proveli isti istraživači. Najprije je procijenjena unutarispitivačka pouzdanost *(engl. intra-observer reliability)*, a zatim i međuispitivačka pouzdanost *(engl. inter-observer reliability)*.

Tijekom prikupljanja podataka ultrazvučno su pregledana oba ramena (n = 148), pri čemu su ramena na neoperiranoj strani služila kao kontrola. Ultrazvučne snimke ramena bile su kodirane i neovisno analizirane, a sve patološke promjene sustavno su dokumentirane. U slučajevima graničnih nalaza postignut je konsenzus između ispitivača, bez potrebe za dodatnim slikovnim metodama. Sva mjerenja provedena su na kodiranim pohranjenim ultrazvučnim snimkama.

Patološki nalazi rotatorne manšete klasificirani su kao tendinoza, kalcificirajuća tendinopatija te djelomične ili potpune rupture. Osteoartritis akromioklavikularnog zgloba klasificiran je prema stupnju težine (blagi, umjereni i teški). Također je zabilježena prisutnost subakromijalno-subdeltoidnog burzitisa te izljeva, tenosinovitisa ili rupture tetive duge glave bicepsa (96).

3.4. Ultrazvučna procjena debljine i ehogenosti kože i potkožnog tkiva

Za potrebe drugog istraživanja tijekom evaluacijskog posjeta provedena je ultrazvučna procjena ispitanica, uključujući pregled dojke, aksilarnih limfnih čvorova i gornjih ekstremiteta. Ultrazvučna mjerenja provedena su uporabom visokofrekventne linearne sonde (9-12 MHz) na ultrazvučnom sustavu SuperSonic Imagine Aixplorer MACH 30 (Aix-en-Provence, Francuska). Podaci potrebni za izračun pouzdanosti mjerenja prikupljeni su istoga dana kao i osnovna mjerenja, a mjerenja su proveli isti ispitivači. Najprije je procijenjena unutarispitivačka pouzdanost (*engl. intra-observer reliability*), a zatim i međuispitivačka pouzdanost (*engl. inter-observer reliability*). Pregled zahvaćenog gornjeg ekstremiteta proveden je radi procjene debljine i ultrazvučnih karakteristika kože i potkožnog tkiva, dok je kontralateralni, nezahvaćeni ekstremitet služio kao kontrola. U početnom mjernom položaju ispitanice su sjedile s nadlakticom blago abduciranom, laktom u potpunoj ekstenziji i šakom u supinaciji. Za petu mjernu točku ispitanice su postavile šaku u pronaciju, oslonjenu dorzalnom stranom. Mjerne točke označene su na pet anatomskih lokalizacija na svakom ekstremitetu pomoću nerastezljive centimetarske vrpce, u skladu s opisima iz literature: medijalna i lateralna strana nadlaktice, 7 cm iznad lakatne brazde; medijalna i lateralna strana podlaktice, 7 cm ispod lakatne brazde; te dorzalna površina šake u sredini udaljenosti između ručnog zgloba i prvog metakarpofalangealnog zgloba (97). Ukupno je analizirano 10 mjernih točaka po ispitanici, pet na svakom gornjem ekstremitetu. Nakon nanošenja sloja gela između sonde i kože, sonda je postavljana okomito na površinu kože uz minimalan pritisak kako bi se izbjegla kompresija mjerenih tkivnih slojeva. Na svakoj mjernoj točki zabilježena je debljina kože i potkožnog tkiva, izražena u centimetrima te uspoređena s odgovarajućom točkom na kontralateralnom ekstremitetu.

Debljina potkožnog tkiva definirana je kao udaljenost između stražnje ehogene granice dermisa i prednje ehogene granice duboke mišićne fascije. Dodatno je procijenjen ultrazvučni obrazac potkožnog tkiva, koji je klasificiran kao „normalan", „fibrozan", „edematozan" ili „bez jasno definirane granice između kože i potkožnog tkiva", prema prethodno predloženoj klasifikaciji (67).

3.5. Ispitivanja pouzdanosti i valjanosti upitnika LYMQoL-UL-CRO u populaciji žena liječenih od raka dojke

Kao što je do sada navedeno, većina ishoda mjerena je jednokratno u sva tri istraživanja, dok je za potrebu treće studije popunjavanje upitnika Lymphedema Quality of Life Questionnaire-Upper Limb - Croatian (LYMQoL-UL-CRO) mjereno dvokratno. Prvo mjerenje provedeno je među 87 ispitanica koje su ispunile hrvatsku verziju upitnika LYMQoL-UL-CRO, Upitnik o zdravstvenom statusu SF-36 *(engl. Short Form-36 Health Survey)* te Numeričku ljestvicu za procjenu intenziteta boli *(engl. Pain Intensity Numerical Rating Scale)*. Uz to, proveden je klinički pregled i mjerenje volumena gornjih ekstremiteta.

Drugo mjerenje, nužno za procjenu test-retest pouzdanosti, provedeno je 10 dana nakon prvog mjerenja kod 68 ispitanica, kada su ispitanice ponovno ispunile upitnik LYMQoL-UL-CRO. U tom razdoblju nisu provođene nove terapijske intervencije koje bi mogle značajno utjecati na stanje limfedema ili kvalitetu života (57, 78, 98). Temeljem ovih podataka napravljena je psihometrijska analiza podataka, detaljno opisana i objavljena u trećem izvornom radu (94).

Upitnik kvalitete života osoba s limfedemom *LYMQoL-Arm, (engl. Lymphedema Quality of Life Questionnaire-Arm)* razvili su u Engleskoj Keeley i suradnici 2010. godine kao bolest specifičan instrument za procjenu kvalitete života povezane sa zdravljem *(engl. Health Related Quality of Life, HRQoL)* u bolesnika s limfedemom gornjeg ekstremiteta (78). Riječ je o upitniku za samoprocjenu koji se sastoji od 21 čestice. Prvih 20 čestica procjenjuju utjecaj limfedema na HRQoL kroz četiri domene: funkciju, izgled, simptome i raspoloženje. Domena funkcije obuhvaća čestice 1-3, pri čemu je čestica 1 dodatno podijeljena na osam podčestica (1a-1h). Domena izgleda uključuje čestice 4-8, domena simptoma čestice 9-14, dok domena raspoloženja obuhvaća čestice 15-20. Svaka se čestica ocjenjuje na četverostupanjskoj Likertovoj ljestvici: nimalo (1), malo (2), prilično (3) ili jako (4), pri čemu viši rezultat označava lošiju kvalitetu života povezanu sa zdravljem. Rezultati pojedinih domena izračunavaju se zbrajanjem odgovora unutar domene i dijeljenjem s brojem odgovorenih čestica. Rezultati za svaku domenu analiziraju se zasebno i usporedno. Ako je više od 50 % čestica unutar pojedine domene ostalo neodgovoreno, rezultat te domene bilježi se kao nula. Posljednja čestica (čestica 21) procjenjuje ukupnu kvalitetu života povezanu sa zdravljem na numeričkoj ljestvici od 0 do 10, gdje 0 označava vrlo lošu, a 10 izvrsnu HRQoL. U ovom istraživanju primijenjena je prevedena i kulturološki prilagođena hrvatska

verzija upitnika, nazvana Lymphedema Quality of Life Questionnaire-Upper Limb - Croatian (LYMQoL-UL-CRO) (78, 79, 86).

Procjena kriterijske valjanosti zahtijeva usporedbu s priznatim zlatnim standardom, pri čemu se u većini istraživanja za tu svrhu koristi upitnik Kratki zdravstveni upitnik s 36 čestica *(engl. Short Form Health Survey-SF-36)* (79, 81). SF-36 je međunarodno priznat instrument za samoprocjenu opće kvalitete života povezane sa zdravljem, za koji postoji validirana hrvatska verzija (99).

Upitnik se sastoji od osam zasebnih ljestvica. Tjelesna komponenta kvalitete života *(engl. Physical Component Summary, PCS)* uključuje domene tjelesnog funkcioniranja (10 čestica), tjelesne boli (2 čestice), ograničenja uloga zbog tjelesnog zdravlja (4 čestice) i opće percepcije zdravlja (5 čestica). Ove domene zajedno procjenjuju tjelesne aspekte kvalitete života povezane sa zdravljem. Mentalna komponenta kvalitete života *(engl. Mental Component Summary, MCS)* obuhvaća vitalnost (4 čestice), socijalno funkcioniranje (2 čestice), ograničenja uloga zbog emocionalnih problema (3 čestice) i mentalno zdravlje (5 čestica), čime se procjenjuju psihološke i socijalne dimenzije kvalitete života povezane sa zdravljem. U ovom istraživanju primijenjena je hrvatska verzija upitnika SF-36. Bodovanje je provedeno prema standardiziranom postupku u tri stupnja, u skladu s uputama iz priručnika za korisnike hrvatske verzije (99, 100). Izračunata su dva sažeta rezultata višeg reda: tjelesna komponenta (PCS) i mentalna komponenta (MCS). Konačan rezultat za svaku domenu i sažete komponente kreće se u rasponu od 0 do 100. Za razliku od upitnika LYMQoL, viši rezultat SF-36 upitnika označava bolju kvalitetu života povezanu sa zdravljem (83, 99).

Za procjenu intenziteta boli korištena je numerička ljestvica intenziteta boli *(engl. Pain Intensity Numerical Rating Scale, PINRS)* s rasponom od 0 do 10, gdje 0 označava odsutnost boli, a 10 najjaču zamislivu bol. Ispitanice su zamoljene da procijene intenzitet boli na temelju vlastitog subjektivnog doživljaja. PINRS je široko korišten, valjan i pouzdan instrument za kvantificiranje subjektivne percepcije boli te je jednostavan za primjenu i lako razumljiv ispitanicima. Viši rezultat označava veći intenzitet boli. U ovom istraživanju ispitanice su pomoću PINRS ljestvice procjenjivale trenutačni i maksimalni intenzitet boli (101).

3.6. Statističke metode

Svi prikupljeni podaci kodirani su, provjereni i pripremljeni za statističku obradu uporabom softverskih alata Microsoft Office Excel 2016 (Microsoft Corporation, Redmond, WA, SAD), IBM SPSS Statistics (verzija 26), JASP (verzija 0.18.3) i statističkog okruženja R. Prije provedbe analize provjerena je potpunost i kvaliteta podataka, a nedostajući podaci obrađeni su metodom višestruke imputacije, pri čemu je generirano pet imputiranih skupova podataka kako bi se smanjila pristranost i povećala statistička snaga analiza.

Distribucija kontinuiranih varijabli ispitana je Kolmogorov-Smirnovljevim testom normalnosti. Kontinuirane varijable koje su slijedile normalnu distribuciju prikazane su kao srednja vrijednost ± standardna devijacija (SD), dok su varijable koje nisu slijedile normalnu distribuciju prikazane kao medijan i interkvartilni raspon (IQR). Kategorijske varijable opisane su apsolutnim i relativnim frekvencijama (broj i postotak).

Usporedbe između skupina za kategorijske varijable provedene su hi-kvadrat testom (χ^2 test). Razlike u kontinuiranim varijablama analizirane su Studentovim t-testom za podatke s normalnom distribucijom, Mann-Whitney U-testom za podatke koji nisu slijedili normalnu distribuciju, dok je Kruskal-Wallisov test korišten pri usporedbi više od dvije skupine. U analizama u kojima je utvrđena nejednakost varijanci primijenjen je Welchov t-test. Za sve statističke analize razina statističke značajnosti postavljena je na $p < 0,05$.

U prvom radu provedena je deskriptivna i inferencijalna statistička analiza podataka korištenjem programa Microsoft Office Excel 2016. Deskriptivna statistika korištena je za prikaz osnovnih demografskih i kliničkih karakteristika ispitanica. Kontinuirane varijable prikazane su kao medijan i interkvartilni raspon (IQR), dok su kategorijske varijable prikazane kao broj i postotak. Usporedbe između skupina za kategorijske varijable provedene su hi-kvadrat testom (χ^2 test), dok su razlike u kontinuiranim varijablama analizirane Studentovim t-testom ili Mann-Whitney U-testom, ovisno o raspodjeli podataka.

U drugom radu analiza je bila usmjerena na procjenu raspodjele podataka, usporedbu skupina te ispitivanje povezanosti ultrazvučno mjerenih parametara s kliničkim ishodima. Raspodjela kontinuiranih varijabli ispitana je jedno-uzorkovanim Kolmogorov-Smirnovljevim testom normalnosti. Varijable s normalnom distribucijom prikazane su kao srednja vrijednost ± standardna devijacija, dok su varijable koje nisu slijedile normalnu distribuciju prikazane kao

medijan i interkvartilni raspon. Kategorijske varijable prikazane su kao frekvencije i postoci. Razlike u kontinuiranim varijablama analizirane su Studentovim t-testom ili Mann-Whitney U-testom, ovisno o raspodjeli podataka.

U okviru analize povezanosti i prediktora kliničkih ishoda (ISL stadij, kategorije opsega ekstremiteta i RVC kategorije) provedene su univarijatne analize radi identifikacije varijabli značajno povezanih s ishodima. Varijable koje su pokazale statističku značajnost ($p < 0,05$) uključene su u višestruke modele. Zbog ograničenog broja ishoda i rizika od prenaučenosti (*overfittinga*) modela primijenjena je LASSO regresija s desetostrukom unakrsnom validacijom za odabir relevantnih prediktora. Na temelju odabranih prediktora konstruirani su dobno prilagođeni višestruki logistički regresijski modeli, a rezultati su prikazani kao omjeri izgleda (OR) s pripadajućim 95 % intervalima pouzdanosti (CI). Interna validacija modela provedena je neparametrijskim *bootstrap* postupkom s 1 000 ponavljanja radi procjene stabilnosti regresijskih koeficijenata. Diskriminacijska sposobnost modela procijenjena je površinom ispod ROC krivulje (AUC), dok je kalibracija modela ispitana Hosmer-Lemeshowljevim testom dobrog slaganja.

U trećem radu provedena je sveobuhvatna psihometrijska i inferencijalna analiza. Interna konzistentnost upitnika procijenjena je Cronbachovim alfa-koeficijentom za svaku pojedinu domenu. Pouzdanost ponovljenog mjerenja (test-retest pouzdanost) procijenjena je izračunom intraklasnog koeficijenta korelacije (ICC) primjenom dvosmjernog modela slučajnih učinaka. Konstrukcijska valjanost ispitana je analizom korelacija između mjernih instrumenata, pri čemu je Spearmanov koeficijent korelacije korišten za varijable koje nisu slijedile normalnu distribuciju, a Pearsonov koeficijent za varijable s normalnom distribucijom. Faktorska struktura instrumenta ispitana je eksploratornom i/ili konfirmatornom faktorskom analizom uz Varimax rotaciju. Prikladnost podataka za faktorsku analizu procijenjena je Kaiser-Meyer-Olkinovom (KMO) mjerom adekvatnosti uzorka i Bartlettovim testom sferičnosti. Također su analizirani podni i stropni efekti, pri čemu su pragovi od 15 % korišteni kao kriterij prihvatljivosti distribucije odgovora.

3.7. Etička načela

Studija iz koje su proizašla sva tri rada provedena je u skladu s etičkim načelima Helsinške deklaracije. Istraživanje je odobrilo Etičko povjerenstvo Kliničkog bolničkog centra Split (broj

protokola: 2181-147/01/06/LJ.Z.-23-2) 28. veljače 2023. godine. Sve ispitanice prije uključivanja u istraživanje dale su dobrovoljni pisani informirani pristanak za sudjelovanje u studiji, nakon što su bile u potpunosti upoznate s ciljem, postupcima i mogućim rizicima istraživanja.

4. SAŽETI PRIIKAZ REZULTATA OBJEDINJENIH RADOVA

Ova disertacija obuhvaća tri vlastita istraživanja usmjerena na objektivnu procjenu mišićno-koštanih i limfnih promjena nastalih nakon liječenja raka dojke te na procjenu kvalitete života žena s limfedemom. Istraživanja se metodološki i tematski nadopunjuju te zajedno pružaju

cjelovit uvid u kliničke, slikovne i subjektivne aspekte sekundarnog limfedema povezanog s rakom dojke (BCRL).

U prvom vlastitom istraživanju analizirana je povezanost boli u ramenu i patoloških ultrazvučnih nalaza u populaciji žena liječenih od raka dojke. Analiza pouzdanosti između i unutar ispitivača pokazala je visoku razinu slaganja, čime je potvrđeno da je ultrazvuk pouzdana i objektivna metoda za procjenu patoloških promjena u području ramena. Klinički izražen kronični limfedem, definiran kao razlika u opsegu gornjih ekstremiteta ≥ 2 cm, bio je prisutan u 35 % ispitanica.

Najvažniji nalaz ove studije bila je snažna i statistički značajna povezanost boli u ramenu s prisutnošću patoloških ultrazvučnih nalaza, osobito patologije tetive supraspinatusa. Suprotno očekivanjima, obilježja onkološkog liječenja, vrsta kirurškog zahvata i prisutnost limfedema nisu pokazali značajan utjecaj na pojavnost boli u ramenu.

Najčešće ultrazvučno identificirane patologije bile su oštećenja tetive supraspinatusa (45 %) i artroza akromioklavikularnog zgloba (35 %). Najčešći pojedinačni nalaz bila je ruptura tetive supraspinatusa (25 %), jednako raspodijeljena na djelomične i potpune rupture, dok su rupture ostalih tetiva bile rijetke. Učestalost patoloških nalaza bila je podjednaka između lijevog i desnog ramena, osim subakromijalno-subdeltoidnog burzitisa, koji je bio značajno češći u desnom ramenu. Bol u ramenu prijavilo je 62 % ispitanica, a patološki ultrazvučni nalaz bio je prisutan u više od 90 % bolnih ramena, u usporedbi s približno 60 % asimptomatskih ramena Utvrđena je jasna povezanost boli i ultrazvučne patologije, dok indeks tjelesne mase, dominantna ruka, obilježja onkološkog liječenja i opseg kirurškog zahvata na aksilarnim limfnim čvorovima nisu pokazali značajan utjecaj. Detaljni rezultati prikazani su u izvornom radu (101).

Drugo vlastito istraživanje bilo je usmjereno na procjenu ultrazvučnih pokazatelja najranijih promjena u razvoju limfedema povezanog s liječenjem raka dojke. Analiza pouzdanosti unutar i između ispitivača pokazala je visoku razinu slaganja, čime je potvrđena objektivnost ultrazvučnih mjerenja debljine kože i potkožnog tkiva.

Ključni nalaz ovog istraživanja pokazao je da je debljina kože mjerena ultrazvukom, osobito u području srednjeg dijela nadlaktice i podlaktice, najsnažniji neovisni pokazatelj prisutnosti i težine limfedema, uključujući i rane stadije bolesti. U žena s ISL II stadijem

limfedema zabilježene su značajno veće razlike u debljini kože te češće povišene vrijednosti ehogenosti potkožnog tkiva u usporedbi s nezahvaćenom rukom. Višestruka logistička regresijska analiza pokazala je da su razlika u debljini kože srednje podlaktice i stražnjeg dijela srednje nadlaktice neovisno povezane s višim ISL stadijem limfedema. Analiza temeljena na relativnom povećanju volumena ruke ≥ 10 % potvrdila je navedene nalaze, dok je primjena nižeg praga (RVC ≥ 5 %) omogućila detekciju ranih i subkliničkih volumenskih promjena. Nakon izrađene višestruke analize i selekcije varijabli, razlika u debljini kože srednje nadlaktice izdvojila se kao jedini neovisni prediktor ranog povećanja volumena ruke, uz približno 1,5 puta veće izglede za prisutnost ranog limfedema. Rezultati su ostali stabilni u analizama osjetljivosti. Detalji su prikazani u izvornom istraživanju (94).

Treće vlastito istraživanje obuhvatilo je prijevod, kulturološku prilagodbu i validaciju upitnika LYMQoL-Arm na hrvatski jezik (LYMQoL-UL-CRO) kod 87 liječenih od raka dojke. Prosječno vrijeme od završetka onkološkog liječenja iznosilo je približno šest godina, a većina sudionica bila je podvrgnuta opsežnijim kirurškim zahvatima.

Psihometrijska analiza pokazala je visoku pouzdanost, dobru valjanost i osjetljivost upitnika na razlike u kliničkom statusu, uz visoku metodološku kvalitetu prema COSMIN *(engl. COnsensus-based Standards for the selection of health Measurement INstruments)* kriterijima. Sve domene upitnika pokazale su dobru unutarnju konzistentnost pri čemu su domene Simptomi i Funkcija imale najviše vrijednosti pouzdanosti. Pouzdanost ponovljenog mjerenja bila je umjerena do dobra, a pokazatelji pogreške mjerenja upućivali su na dobru osjetljivost instrumenta na promjene.

Valjanost upitnika potvrđena je kriterijskom, konstrukcijskom i diskriminativnom analizom. Upitnik je uspješno razlikovao žene s različitim stupnjem limfedema, osobito pri ranom povećanju volumena ruke ≥ 5 %, pri čemu su zabilježeni značajno lošiji rezultati u domenama Funkcija, Simptomi i Raspoloženje. Sudionice su upitnik ocijenile jasnim, kratkim i primjerenim, uz prosječno vrijeme ispunjavanja od oko pet minuta. Detaljan prikaz rezultata objavljen je u izvornom radu (99).

5. RASPRAVA

Rezultati naših istraživanja pružaju integrirani uvid u kliničke, ultrazvučne i funkcionalne karakteristike subakromijalnog bolnog sindroma i limfedema gornjeg ekstremiteta u dugotrajnoj fazi nakon liječenja raka dojke. Za razliku od većine dosadašnjih istraživanja koja su pojedine

aspekte promatrala izolirano, ova disertacija objedinjuje kliničke, ultrazvučne, funkcionalne i samoprijavljene pokazatelje u jedinstven analitički okvir.

U cjelini, disertacija donosi tri središnja doprinosa. Prvi doprinos pokazuje da su ultrazvučno utvrđene patologije rotatorne manšete česte, često bilateralne i nerijetko asimptomatske. Drugi doprinos identificira debljinu kože, osobito u području medijalnog dijela nadlaktice, kao osjetljiv ultrazvučni marker ranih promjena povezanih s limfedemom pri nižem volumenskom pragu (RVC ≥ 5%). Treći doprinos odnosi se na validaciju instrumenta LYMQoL-UL-CRO, čime je prvi put u hrvatskom kontekstu osiguran standardizirani alat za procjenu subjektivnog tereta limfedema i kvalitete života.

Utvrđene mišićno-koštane promjene u području ramena, zajedno s ultrazvučno verificiranim strukturnim nalazima, ukazuju na složen odnos između objektivnih oštećenja i subjektivno doživljene boli (96). Ovi rezultati doprinose boljem razumijevanju mehanizama nastanka simptoma te naglašavaju važnost pravodobne dijagnostike i ciljanih rehabilitacijskih intervencija.

Slično tome, dobiveni podaci o limfedemu potvrđuju njegovu kliničku heterogenost i potrebu za osjetljivijim metodama koje omogućuju rano prepoznavanje. Ultrazvučna procjena pokazala se korisnim alatom za otkrivanje promjena u koži i potkožnom tkivu, pružajući dodatne informacije u odnosu na standardne kliničke mjere (89).

Osim objektivnih kliničkih pokazatelja, rezultati validacije hrvatske verzije upitnika LYMQoL-Arm (LYMQoL-UL-CRO) omogućili su pouzdanu procjenu subjektivnog tereta bolesti. Analiza odnosa između objektivnih nalaza i samoprocijenjenih ishoda dodatno je rasvijetlila kompleksnu povezanost tjelesnih promjena i kvalitete života, naglašavajući važnost biopsihosocijalnog pristupa u dugotrajnoj skrbi žena liječenih od raka dojke. Važno je pritom naglasiti da i minimalne objektivne promjene mogu biti praćene klinički relevantnim simptomima i ograničenjima koja žene doživljavaju kao značajan teret u svakodnevnom funkcioniranju (94).

U nastavku rasprave rezultati će se interpretirati u kontekstu postojećih znanstvenih spoznaja, uz razmatranje njihovih kliničkih implikacija i mogućih smjernica za unaprjeđenje rehabilitacijskih protokola. U cjelini, rezultati ukazuju da su bol u ramenu, strukturne promjene

rotatorne manšete, rane promjene u debljini kože i narušena kvaliteta života međusobno povezane, ali ne i linearno uzročno uvjetovane pojave, što naglašava potrebu za opreznom interpretacijom nalaza, osobito u kontekstu presječnog dizajna istraživanja.

Jedan od središnjih nalaza disertacije, objavljen u prvom radu, jest da naši rezultati potvrđuju visoku učestalost patologija rotatorne manšete kod žena nakon liječenja raka dojke. Međutim, ključan doprinos rada nije samo potvrda njihove učestalosti, već nalaz podjednake zastupljenosti promjena na operiranoj i neoperiranoj strani. Takvi nalazi naglašavaju složenost nastanka boli u ramenu u ovoj populaciji te potrebu za multidisciplinarnim pristupom u dijagnostici i rehabilitaciji, u kojem ultrazvuk ima važnu ulogu, ali se njegovi nalazi trebaju interpretirati u kontekstu kliničkog pregleda i funkcionalne procjene (96).

Kronična bol u ramenu predstavlja jedan od najčešćih i klinički najznačajnijih ishoda liječenja raka dojke te može značajno utjecati na funkcionalnu sposobnost i kvalitetu života liječenih žena (20). Subakromijalni bolni sindrom (SBS) obuhvaća skup stanja koja izazivaju bol u području ramena (28, 36, 95). S obzirom na višekomponentnu etiologiju, simptomi se mogu razviti kao posljedica kombinacije strukturnih promjena i funkcionalnih poremećaja gornjeg ekstremiteta, uključujući promjene na tetivama i burzama, mišićnu disfunkciju te suženje subakromijalnog prostora (33, 39).

U literaturi se navodi da su žene nakon mastektomije, disekcije aksilarnih limfnih čvorova, radioterapije i drugih terapijskih modaliteta izložene povećanom riziku za razvoj disfunkcije gornjeg ekstremiteta, uključujući bol, smanjen opseg pokreta i limfedem (9, 10, 21, 26). U populaciji žena liječenih od raka dojke subakromijalni bolni sindrom poprima dodatnu kliničku važnost zbog specifičnih posljedica onkološkog liječenja. Iako navedene terapijske metode same po sebi ne moraju uzrokovati primarno strukturno oštećenje ramenog zgloba, funkcionalne promjene u kinetici i skapulotorakalnoj koordinaciji mogu posljedično dovesti do klinički značajne boli i funkcionalnih ograničenja (33, 36, 39, 102). Takve funkcionalne promjene smatraju se jednim od mogućih mehanizama koji mogu doprinijeti razvoju SBS-a u ovoj populaciji (39, 103, 104).

Međutim, u našem istraživanju nije utvrđena povezanost limfedema niti vrste operativnog zahvata sa strukturnim promjenama u području ramena. Ovakav nalaz može se objasniti

presječnim dizajnom studije te heterogenošću vremena proteklog od operacije među ispitanicama. Stoga su za donošenje pouzdanijih zaključaka potrebna prospektivna istraživanja koja bi omogućila praćenje razvoja boli, funkcionalnih i strukturnih promjena ramena u odnosu na limfedem i druge čimbenike povezane s liječenjem raka dojke.

U našem istraživanju utvrđena je visoka učestalost ultrazvukom otkrivenih strukturnih promjena u području ramena. Najčešće promjene odnosile su se na tetivu m. supraspinatusa, dok je osteoartritis akromioklavikularnog zgloba bio drugi najčešći nalaz. Ovakav obrazac u skladu je s nalazima iz opće populacije, u kojoj su degenerativne promjene rotatorne manšete, osobito m. supraspinatusa, česte i kod osoba koje nikada nisu tražile medicinsku pomoć zbog problema s ramenom (28, 37, 39, 41). Važno je naglasiti da su u našem uzorku rupture tetive supraspinatusa bile najčešći patološki nalaz, pri čemu su zabilježene i parcijalne i potpune rupture. Budući da je u literaturi istaknuto kako osobito potpune rupture imaju veći potencijal za funkcionalno oštećenje, ovakvi nalazi mogu biti klinički relevantni, no njihovo značenje potrebno je interpretirati u širem kliničkom kontekstu (41, 105).

Najvažniji nalaz ovog istraživanja jest da su patološki ultrazvučni nalazi bili podjednako zastupljeni na operiranoj i neoperiranoj strani, bez statistički značajne razlike u učestalosti i tipu promjena između ramena na strani operacije i kontrolne strane. Ovaj rezultat upućuje na to da se pronađene strukturne promjene ne mogu jednostavno pripisati isključivo kirurškom zahvatu ili onkološkom liječenju, nego je vjerojatno da barem dio nalaza odražava dobno uvjetovane degenerativne promjene, osobito u populaciji srednje i starije životne dobi (40, 105, 106). Dodatno, u značajnom broju slučajeva patološki ultrazvučni nalazi bili su prisutni i u ramenima bez boli, što potvrđuje poznatu činjenicu da se strukturne promjene rotatorne manšete često nalaze i kod asimptomatskih osoba (103, 106). To dodatno naglašava da ultrazvuk, iako vrijedan u otkrivanju strukturnih promjena, ne može samostalno objasniti etiologiju boli ni biti jedina osnova za dijagnostičko zaključivanje.

U našoj studiji kod većine žena s prisutnom boli ultrazvučno je potvrđena patologija, što sugerira da strukturne promjene u području rotatorne manšete često prate simptomatologiju. Međutim, činjenica da je velik udio asimptomatskih ramena također pokazivao patološke nalaze upućuje na ograničenu specifičnost slikovne dijagnostike u objašnjenju boli. U tom smislu,

subakromijalni bolni sindrom treba promatrati kao multifaktorijalno stanje pri čemu klinički simptomi mogu proizlaziti iz kombinacije strukturnih promjena, biomehaničkih adaptacija, neuromuskularne disfunkcije te drugih fizičkih i psiholoških čimbenika (104). Stoga se potvrđuje potreba za interpretacijom ultrazvučnih nalaza u integraciji s kliničkim pregledom i funkcionalnom procjenom, a ne izolirano.

U našem istraživanju nije utvrđena povezanost između boli u ramenu i poznatih čimbenika rizika, uključujući vrstu operativnog zahvata, radioterapiju, kemoterapiju, endokrinu terapiju, indeks tjelesne mase, dominantnu ruku i prisutnost limfedema. Posebno je važno istaknuti da klinički dijagnosticiran limfedem, iako se često navodi kao potencijalni čimbenik povezan s disfunkcijom ramena, u našem uzorku nije bio povezan s većom prevalencijom boli (9, 24, 107). Istodobno, odnos limfedema i ultrazvučno potvrđenih strukturnih promjena ramena u ovom presječnom dizajnu nije moguće pouzdano razjasniti, što dodatno naglašava potrebu za prospektivnim istraživanjima.

Jedno od mogućih objašnjenja ovakvih nalaza jest da bol i disfunkcija ramena u ovoj populaciji ne proizlaze nužno izravno iz strukturnih promjena, nego mogu biti povezane s dugoročnim adaptacijama nakon liječenja, uključujući promjene posture, promijenjene obrasce kretanja i kompenzacijsko opterećenje kontralateralne strane (108-110). Nadalje, ranija istraživanja upućuju na mogućnost bilateralne morbidnosti nakon liječenja raka dojke, što može biti posljedica sistemskih mehanizama ili mehaničkog preopterećenja kontralateralnog ramena (110, 111). Ovakav koncept dodatno podupire naše rezultate koji pokazuju podjednaku zastupljenost patoloških nalaza na obje strane.

Klinička implikacija ovih nalaza jest da ultrazvuk ima važnu ulogu u identifikaciji strukturnih promjena, ali ne smije biti jedina osnova za dijagnostičko zaključivanje. Interpretacija nalaza mora biti integrirana s kliničkim pregledom i funkcionalnom procjenom.

Drugi rad disertacije usmjeren je na ultrazvučnu procjenu debljine kože i potkožnog tkiva kao potencijalnih markera za rano prepoznavanje limfedema povezanog s liječenjem raka dojke. Polazeći od činjenice da se limfedem u kliničkoj praksi i dalje najčešće prepoznaje tek nakon pojave jasno vidljive otekline zahvaćenog dijela tijela, cilj istraživanja bio je procijeniti može li

ultrazvuk otkriti tkivne promjene u fazi kada standardne volumne i konvencionalne metode još ne pokazuju dovoljno jasne znakove bolesti (87, 112).

Ključni nalaz ove studije jest da se ultrazvukom mjerljiva promjena debljine kože može otkriti u ranom stadiju limfedema, osobito kod žena s minimalnim volumnim promjenama (RVC ≥ 5 %) koje se u mnogim kliničkim okruženjima još uvijek ne prepoznaju kao jasna dijagnostička kategorija (87, 89). U našem uzorku višestruka logistička regresijska analiza pokazala je da je povećanje debljine kože u medijalnom dijelu nadlaktice *(engl. upper arm medial cutis)* statistički značajno povezano s povećanjem volumena ruke od ≥ 5 % (OR 1,49; p = 0,047), što ovu mjernu točku ističe kao potencijalno posebno osjetljiv rani marker (89). Ovaj nalaz ima posebnu kliničku vrijednost jer pomiče dijagnostički fokus s kasnih, volumenski izraženih stadija prema ranim, subkliničkim fazama bolesti.

Dobiveni rezultati podupiru koncept da limfedem nije nagli događaj, već postupno progresivan proces obilježen kontinuiranim promjenama tkivne strukture. U tom smislu, rani stadiji bolesti mogu biti prisutni prije pojave jasno vidljivih kliničkih znakova, što je u skladu s patofiziološkim modelima u kojima u početku dominira nakupljanje međustanične tekućine, nakon čega slijedi postupni razvoj fibroze i promjene arhitekture potkožnog tkiva (44, 53, 65, 113, 114).

Klinička praksa oslanja se na mjerenje opsega i volumena ekstremiteta, no usporedbe metoda pokazale su da se različiti kriteriji mogu značajno razlikovati po osjetljivosti i specifičnosti (54, 71, 90, 115). Posebno je važno istaknuti da standardne volumne metode ne razlikuju uzrok promjene, odnosno ne mogu pouzdano razlučiti radi li se primarno o nakupljanju tekućine ili o patološkoj proliferaciji i remodeliranju tkiva, što može dovesti do pogrešnog tumačenja ranih promjena (22, 56, 65). U tom dijagnostičkom kontekstu ISL klasifikacija ostaje važan klinički okvir, no stadij 0 (subklinički limfedem) često se oslanja na subjektivnu percepciju pacijentice i suptilne promjene koje je teško standardizirati. U tom smislu ultrazvuk može imati važnu ulogu kao objektivna metoda za potvrdu ili isključenje ranih tkivnih promjena u koži i potkožnom tkivu (87, 91, 116).

U našem uzorku prag RVC ≥ 5 % pokazao se korisnim za otkrivanje rane kliničke faze, što je u skladu sa suvremenim modelima praćenja koji naglašavaju važnost rane intervencije (50, 64, 67, 93, 112). Također, u literaturi se navodi da se prag RVC ≥ 10 % i dalje često koristi kao

konzervativniji kriterij, no takav pristup može propustiti rane slučajeve i time odgoditi početak intervencije (52, 71, 117).

Naši rezultati dodatno ukazuju na razlike u ultrazvučnim pokazateljima između ranih i uznapredovalih stadija bolesti: debljina kože u određenim anatomskim točkama, osobito u području medijalne nadlaktice, bila je povezana s ranim volumnim promjenama, dok promjene potkožnog tkiva (debljina i ehogenost) više odražavaju uznapredovalije stadije limfedema (49, 50, 53, 67, 89). Time se sugerira potencijalna uloga ultrazvuka ne samo u dijagnostici, nego i u praćenju progresije bolesti (61, 67, 97, 116, 118). Standardizacija mjerenja pritom je nužan preduvjet za širu kliničku primjenu ultrazvuka u praćenju limfedema, ali i za usporedivost budućih istraživanja (117).

Pronađeni obrazac nalaza ima i anatomsko objašnjenje. Medijalni dio nadlaktice predstavlja područje limfne drenaže koja izravno komunicira s aksilarnim limfnim čvorovima, koji su često zahvaćeni kirurškim uklanjanjem ili radioterapijom (70, 113). Nadalje, lateralni limfni putevi mogu ostati očuvani i predstavljati kompenzacijski drenažni put, što može objasniti zašto lateralne točke mjerenja nisu pokazale jednaku osjetljivost (121).

Naši se rezultati uklapaju i u ranija istraživanja koja su pokazala da se rani simptomi limfedema često manifestiraju kao osjećaj punoće ili težine u nadlaktici, čak i kada ukupni volumen ruke ostaje unutar granica normale. Time se potvrđuje da subjektivni simptomi mogu prethoditi klinički mjerljivim promjenama volumena, ali i da se mogu bolje objektivizirati slikovnim metodama koje procjenjuju lokalne promjene tkiva (53, 77, 91, 116). U odnosu na dosadašnju literaturu, nalaz da je medijalni dio nadlaktice posebno važan za ranu detekciju djelomično odstupa od nekih ranijih ultrazvučnih studija koje su češće naglašavale podlakticu kao početno mjesto promjena. Moguće je da te razlike proizlaze iz različitih dijagnostičkih pragova i heterogenih definicija subkliničkog limfedema, što ostaje jedan od ključnih metodoloških problema u postojećoj literaturi (62, 72, 122-124).

Iako ultrazvučni nalazi pružaju objektivan uvid u rane strukturne promjene povezane s limfedemom, oni sami po sebi ne obuhvaćaju u potpunosti subjektivni teret bolesti i njezin utjecaj na svakodnevno funkcioniranje žena koje su preživjele rak dojke (53, 76, 116). Klinički gledano,

ovi rezultati podupiru uključivanje ultrazvuka u modele praćenja rizičnih žena, osobito u situacijama kada su volumenske promjene minimalne, ali su simptomi već prisutni.

Treći temeljni doprinos ove disertacije ima dvostruku vrijednost: metodološku, jer omogućuje standardizirano mjerenje kvalitete života u hrvatskoj populaciji, i kliničku, jer uvodi sustavnu procjenu subjektivnog tereta bolesti u rehabilitacijsku praksu. Prvi doprinos odnosi se na prijevod, kulturološku prilagodbu i validaciju hrvatske verzije upitnika LYMQoL-Arm (LYMQoL-UL-CRO). Ovaj rad predstavlja ključnu poveznicu između objektivnih kliničkih i slikovnih nalaza te subjektivnog doživljaja bolesti u populaciji žena liječenih od raka dojke (94). Instrument pokazuje snažna psihometrijska svojstva, potvrđenu četverofaktorsku strukturu te sposobnost razlikovanja ranih stadija limfedema, čime se omogućuje standardizirana i pacijentici usmjerena procjena ishoda. Njegova primjena može unaprijediti kliničko praćenje, olakšati donošenje rehabilitacijskih odluka te podržati aktivne modele praćenja i intervencije u dugoročnom zbrinjavanju žena nakon liječenja raka dojke (94).

U suvremenoj rehabilitacijskoj i onkološkoj skrbi sve se više naglašava potreba za integriranjem instrumenata koji mjere samoprijavljene ishode *(engl. Patient Reported Objective Measures - PROM)* u kliničku praksu, osobito kod kroničnih bolesti kao što je limfedem (74). Premda generički instrumenti, poput SF-36, mogu pružiti korisne informacije o općem zdravstvenom statusu, oni često ne uspijevaju obuhvatiti specifične i višedimenzionalne posljedice limfedema, kao što su osjećaj težine, napetosti, funkcionalna ograničenja, promjene tjelesne slike i emocionalno opterećenje (76, 125, 126). Upravo zbog toga razvijeni su bolesti specifični instrumenti poput LYMQoL-a, koji omogućuju detaljniju procjenu kvalitete života povezane s limfedemom.

LYMQoL upitnik izvorno je razvijen kao bolest specifičan PROM za procjenu kvalitete života u bolesnika s limfedemom gornjeg i donjeg ekstremiteta. U dosadašnjoj literaturi instrument je pokazao dobra psihometrijska svojstva u brojnim kulturnim adaptacijama, uključujući Italiju, Švedsku, Tursku, Ujedinjeno Kraljevstvo, Koreju, Kinu i Nizozemsku, pri čemu se konzistentno potvrđuju njegova klinička korisnost i stabilnost faktorske strukture (63, 78, 79, 81, 83, 84, 127). Rezultati našeg istraživanja potvrdili su ključna psihometrijska svojstva hrvatske verzije LYMQoL-UL-CRO. Sve domene upitnika pokazale su zadovoljavajuću do visoku unutarnju

konzistentnost, pri čemu su domene Simptomi i Funkcija imale najviše vrijednosti (Cronbach α = 0,91 i 0,85), dok je domena Raspoloženje u inicijalnom testiranju imala nešto nižu, ali i dalje prihvatljivu pouzdanost (α = 0,75), koja se u postupku ponovljenog mjerenja (test-retest) dodatno poboljšala. Dobiveni rezultati upućuju na stabilnost konstrukta kvalitete života povezanog s limfedemom, neovisno o kulturnom kontekstu. Time je omogućena pouzdana usporedivost rezultata hrvatske populacije s međunarodnim istraživanjima, ali i standardizirana primjena u kliničkoj praksi (94).

Analiza test-retest pouzdanosti u našem istraživanju pokazala je umjerenu pouzdanost (ICC 0,68–0,73), uz nešto nižu stabilnost domene vezane uz izgled. Smatramo da takav rezultat može biti posljedica svakodnevnih fluktuacija volumena ruke u blažim stadijima limfedema, ali i promjenjive percepcije izgleda, koja je osjetljiva na trenutačno stanje otekline, emocionalno stanje te promjene tjelesne slike (73, 79, 81, 91). Dodatno, analiza pogreške mjerenja pokazala je niske vrijednosti SEM-a i SRD-a u svim domenama, što potvrđuje da instrument ima dobru preciznost te može razlikovati stvarne promjene u simptomima i funkcionalnom statusu od promjena koje proizlaze iz slučajne varijabilnosti mjerenja (94).

Strukturna valjanost instrumenta potvrđena je eksploratornom faktorskom analizom, pri čemu je dobivena četverofaktorska struktura (Funkcija, Izgled, Simptomi, Raspoloženje), koja objašnjava 60,49 % ukupne varijance, uz vrlo dobru prikladnost podataka za faktorsku analizu (KMO = 0,89; Bartlett $p < 0,001$). Time se potvrđuje konceptualna stabilnost LYMQoL konstrukta kvalitete života povezanog s limfedemom, neovisno o kulturološkom kontekstu (94).

Konstruktna i kriterijska valjanost dodatno su potvrđene analizom povezanosti s generičkim instrumentom SF-36. Očekivano, domene Funkcija i Simptomi pokazale su snažne negativne korelacije s fizičkom komponentom SF-36 (PCS), dok je domena Raspoloženje pokazala umjerenu negativnu korelaciju s mentalnom komponentom SF-36 (MCS). Takav obrazac korelacija teorijski je konzistentan, budući da veće funkcionalno ograničenje i veći simptomatski teret moraju rezultirati lošijom percepcijom fizičkog zdravlja, dok emocionalni aspekti limfedema imaju izraženiji odnos s mentalnim zdravljem (77, 94). Domena Izgled nije pokazala statistički značajne korelacije s komponentama SF-36, što se može objasniti činjenicom da generički instrumenti nedovoljno obuhvaćaju specifično estetske i aspekte slike tijela povezane s

limfedemom, iako oni čine važan dio iskustva bolesti kod žena koje su preživjele rak dojke (52, 77, 128).

Posebno značajan nalaz ovog rada odnosi se na diskriminativnu valjanost instrumenta (77). LYMQoL-UL-CRO uspješno je razlikovao skupine žena s minimalnim volumenskim povećanjem (RVC < 5 %) od onih s klinički definiranim ranim limfedemom (RVC ≥ 5 %). U skupini s RVC ≥ 5 % zabilježeni su statistički značajno lošiji rezultati u domenama Funkcija, Simptomi i Raspoloženje, dok razlike u domeni Izgled nisu bile statistički značajne (55, 70, 85). Ovaj nalaz potvrđuje da instrument može otkriti narušenu kvalitetu života i u fazi kada su volumenske promjene relativno male, ali klinički relevantne (98).

Naši rezultati dodatno potvrđuju koncept da subjektivni teret bolesti ne ovisi isključivo o objektivnim kliničkim pokazateljima (78, 86). U radu se ističe da se ukupna kvaliteta života, mjerena generičkim instrumentom SF-36, nije značajno razlikovala između skupina s RVC < 5 % i RVC ≥ 5 %, što sugerira da volumen ekstremiteta nije jedini niti dominantni čimbenik dobrobiti. Naprotiv, simptomi poput osjećaja težine, napetosti, boli i funkcionalnih ograničenja mogu imati izraženiji utjecaj na svakodnevno funkcioniranje i emocionalnu prilagodbu nego sama mjera volumena (129, 130). Ovakav nalaz naglašava ograničenja oslanjanja isključivo na objektivne mjere u procjeni ukupnog tereta limfedema te podupire potrebu za integracijom subjektivnih i objektivnih pokazatelja u model praćenja žena nakon liječenja raka dojke (55, 73).

U radu se naglašava da je prag RVC ≥ 5 % niži od tradicionalnog kriterija od ≥ 10 %, koji se često koristi za definiranje „klinički evidentnog" limfedema, no upravo takav konzervativniji pristup može propustiti rane slučajeve i odgoditi intervenciju (21, 78, 81).

Takav nalaz dodatno naglašava ograničenje oslanjanja isključivo na objektivne mjere u procjeni ukupnog tereta limfedema te podupire potrebu za integracijom subjektivnih i objektivnih pokazatelja u modele praćenja žena nakon liječenja raka dojke (55, 73).

Kao klinička implikacija, uključivanje upitnika LYMQoL-UL-CRO u rutinsko praćenje omogućuje rano prepoznavanje subjektivnog tereta i praćenje učinka rehabilitacije, osobito u stadijima kada volumenske promjene nisu dominantne, ali su simptomi i funkcionalna ograničenja već prisutni.

U kontekstu ove disertacije, rezultati trećeg rada dodatno osnažuju koncept integriranog pristupa skrbi za žene koje su preživjele rak dojke. Zajednička interpretacija nalaza triju istraživanja pokazuje da mišićno-koštane promjene ramena, limfedem i kvaliteta života ne predstavljaju odvojene entitete, već međusobno povezane komponente istog kliničkog spektra dugoročnih posljedica liječenja raka dojke. Bol u ramenu, funkcionalna ograničenja i limfne promjene često koegzistiraju, međusobno se pojačavaju i kumulativno narušavaju svakodnevno funkcioniranje žena liječenih od raka dojke. Stoga se optimalan model skrbi treba temeljiti na integraciji slikovnih, funkcionalnih i samoprijavljenih pokazatelja, a ne na izoliranom oslanjanju na pojedinu dijagnostičku metodu.

Iako dobiveni nalazi pružaju važne uvide u dugoročne posljedice liječenja raka dojke, njihovu interpretaciju potrebno je sagledati u kontekstu metodoloških ograničenja korištenih istraživačkih pristupa.

Sva tri istraživanja uključena u disertaciju imaju presječni (*engl. cross-sectional*) dizajn, što onemogućuje donošenje zaključaka o uzročno-posljedičnim odnosima između liječenja raka dojke, ultrazvučno potvrđenih strukturnih promjena ramena, razvoja limfedema gornjeg ekstremiteta i promjena kvalitete života. Iako su utvrđene značajne povezanosti između promatranih varijabli, ovakav dizajn ne omogućuje uvid u vremenski slijed nastanka promjena ni njihovu progresiju kroz vrijeme.

Nadalje, istraživanja su provedena u jednom kliničkom centru, što može ograničiti primjenjivost rezultata na širu populaciju žena koje su preživjele rak dojke. Specifičnosti lokalne kliničke prakse, rehabilitacijskih protokola i organizacije skrbi mogle su utjecati na učestalost i izraženost uočenih nalaza. Ipak, relativno homogeni uzorak i jasno definirani kriteriji uključenja doprinose unutarnjoj valjanosti studija.

Veličina uzorka, iako usporediva ili veća u odnosu na većinu dosadašnjih ultrazvučnih studija u ovoj populaciji, može biti nedostatna za detekciju manje izraženih učinaka, osobito u multivarijatnim analizama i unutar specifičnih podskupina ispitanica. Zbog ograničenog broja ishoda pojedini potencijalno relevantni čimbenici, poput indeksa tjelesne mase, vrste potporne terapije ili vrste aksilarne kirurgije, nisu mogli biti uključeni u sve statističke modele bez rizika od preopterećenja modela.

Iako je ultrazvučna dijagnostika pokazala dobru pouzdanost mjerenja, uključujući visoku međuispitivačku i unutarispitivačku pouzdanost, ultrazvuk ostaje metoda ovisna o iskustvu stručnjaka koji je izvodi. Unatoč primjeni standardiziranih protokola i analizi snimljenih slika od strane iskusnih ispitivača, određeni stupanj subjektivnosti u interpretaciji nalaza ne može se u potpunosti isključiti. Osim toga, ultrazvučna procjena ograničena je na morfološke promjene te ne pruža izravan uvid u funkcionalni status limfnog sustava.

Dijagnostika limfedema temeljila se na kombinaciji volumnih mjerenja, kliničkih kriterija i ultrazvučnih pokazatelja. Iako su korišteni pragovi u skladu s postojećom literaturom, još uvijek ne postoji općeprihvaćen zlatni standard za ranu dijagnozu limfedema povezanog s liječenjem raka dojke. Ta heterogenost dijagnostičkih kriterija može otežati usporedbu rezultata s drugim studijama i utjecati na interpretaciju ranih stadija bolesti.

Procjena kvalitete života temeljila se na samoprocjeni ispitanica, što nosi rizik od pristranosti, uključujući utjecaj trenutačnog emocionalnog stanja, adaptacijskih mehanizama i socijalnog konteksta. Iako je korišten validiran i psihometrijski pouzdan instrument, rezultati kvalitete života ne mogu se izravno uspoređivati s objektivnim kliničkim pokazateljima.

Naposljetku, disertacija nije uključivala longitudinalnu evaluaciju terapijskih intervencija, zbog čega nije bilo moguće procijeniti kako rani ultrazvučni nalazi utječu na ishod liječenja, progresiju limfedema, funkcionalni oporavak ramena ili promjene kvalitete života nakon ciljane rehabilitacije. Ovaj nedostatak ujedno predstavlja važan poticaj za buduća istraživanja.

6. ZAKLJUČCI

Na temelju provedenih istraživanja i dobivenih rezultata mogu se izvesti sljedeći zaključci:

Dugoročne posljedice liječenja raka dojke predstavljaju složen i višedimenzionalan zdravstveni problem. Strukturne mišićno-koštane promjene 3u području ramena, razvoj limfedema gornjeg ekstremiteta i narušena kvaliteta života često su prisutni kod žena koje su preživjele rak dojke te čine međusobno povezane aspekte istog kliničkog spektra postterapijskih komplikacija.

Ultrazvučna dijagnostika pokazala se pouzdanom, neinvazivnom i objektivnom metodom za identifikaciju patoloških promjena u području ramena kod žena liječenih od raka dojke. Najčešći nalaz bila je patologija tetive m. supraspinatusa, što potvrđuje važnu ulogu ultrazvuka u procjeni mišićno-koštanih promjena kod pacijentica s bolnim ramenom.

Podjednaka učestalost patoloških ultrazvučnih nalaza na operiranoj i neoperiranoj strani te njihova prisutnost u dijelu asimptomatskih ramena upućuju na to da ultrazvučni nalaz sam po sebi ne može objasniti etiologiju boli. Stoga se slikovni nalazi moraju tumačiti u kontekstu kliničkog pregleda i funkcionalne procjene, što naglašava potrebu za integriranim i multidisciplinarnim pristupom procjeni i rehabilitaciji bolnog ramena u ovoj populaciji.

Limfedem povezan s liječenjem raka dojke razvija se postupno, a rane promjene u strukturi kože i potkožnog tkiva moguće je objektivno detektirati ultrazvučnom dijagnostikom prije pojave klinički vidljivog edema. Debljina kože, osobito u području medijalne nadlaktice predstavlja osjetljiv ultrazvučni marker ranih stadija limfedema, uključujući minimalne volumne promjene (RVC $\geq$ 5 %).

Primjena nižeg volumenskog praga (RVC $\geq$ 5 %) omogućuje prepoznavanje ranih stadija limfedema koje bi prema tradicionalnim dijagnostičkim kriterijima često ostali neprepoznati, čime se otvara mogućnost ranijeg započinjanja preventivnih i rehabilitacijskih intervencija te potencijalnog usporavanja progresije bolesti.

Validacijom hrvatske verzije upitnika LYMQoL-UL-CRO potvrđena su dobra psihometrijska svojstva instrumenta, uključujući visoku unutarnju konzistentnost, zadovoljavajuću test-retest pouzdanost i dobru konstruktivnu valjanost, čime je omogućena standardizirana procjena kvalitete života žena s limfedemom gornjeg ekstremiteta u hrvatskom kliničkom i istraživačkom okruženju.

Rezultati istraživanja pokazuju da subjektivni teret bolesti može biti izražen već u ranim stadijima limfedema, čak i kada su objektivne volumne promjene minimalne. Integracija ultrazvučne procjene, funkcionalne evaluacije ishoda prijavljenih od strane pacijentica predstavlja važan temelj za razvoj ciljanih i pravodobnih rehabilitacijskih pristupa usmjerenih na očuvanje funkcije i kvalitete života žena liječenih od raka dojke.

Buduća prospektivna i longitudinalna istraživanja potrebna su kako bi se bolje razjasnio vremenski slijed razvoja mišićno-koštanih i limfnih komplikacija, procijenila njihova progresija te utvrdila učinkovitost ranih dijagnostičkih i rehabilitacijskih intervencija koje se temelje na kombinaciji objektivnih i subjektivnih pokazatelja.

7. LITERATURA

1. World Health Organization. Breast cancer [Internet]. Geneva: WHO; 2025 Aug 14 [cited 2026 Mar 9]. Available from: https://www.who.int/news-room/fact-sheets/detail/breast-cancer

2. Hrvatski zavod za javno zdravstvo. Incidencija raka u Hrvatskoj u 2023. godini [Internet]. Zagreb: HZJZ; 2025 Dec 23 [cited 2026 Mar 9]. Available from: https://www.hzjz.hr/periodicne-publikacije/incidencija-raka-u-hrvatskoj-u-2023-godini/

3. Liu PH, Wei JC, Wang YH, Yeh MH. Female breast cancer incidence predisposing risk factors identification using nationwide big data: a matched nested case-control study in Taiwan. BMC Cancer. 2022;22(1):849.

4. Bray F, Laversanne M, Sung H, Ferlay J, Siegel RL, Soerjomataram I, et al. Global cancer statistics 2022: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 2024;74(3):229-63.

5. Kashyap D, Pal D, Sharma R, Garg VK, Goel N, Koundal D, et al. Global increase in breast cancer incidence: risk factors and preventive measures. Biomed Res Int. 2022;2022:9605439.

6. Łukasiewicz S, Czeczelewski M, Forma A, Baj J, Sitarz R, Stanisławek A. Breast cancer: epidemiology, risk factors, classification, prognostic markers, and current treatment strategies—an updated review. Cancers (Basel). 2021;13(17):4287.

7. Waks AG, Winer EP. Breast cancer treatment: a review. JAMA. 2019;321(3):288-300. doi:10.1001/jama.2018.19323.

8. Ben-Dror J, Shalamov M, Sonnenblick A. The history of early breast cancer treatment. Genes (Basel). 2022;13(6):960.

9. Hidding JT, Beurskens CH, van der Wees PJ, van Laarhoven HW, Nijhuis-van der Sanden MW. Treatment-related impairments in arm and shoulder in patients with breast cancer: a systematic review. PLoS One. 2014;9(5):e96748.

10. Hayes S, Cornish B, Newman B. Comparison of methods to diagnose lymphoedema among breast cancer survivors: 6-month follow-up. Breast Cancer Res Treat. 2005;89(3):221-6.

11. Khajoei R, Ilkhani M, Azadeh P, Zohari Anboohi S, Heshmati Nabavi F. Breast cancer survivors-supportive care needs: systematic review. BMJ Support Palliat Care. 2023;13(2):143-53.

12. Brauer ER, Ganz PA. Moving the translational needle in breast cancer survivorship: connecting intervention research to clinical practice. J Clin Oncol. 2022;40(19):2069-73.

13. Pinto M, Calafiore D, Piccirillo MC, Costa M, Taskiran OO, de Sire A. Breast cancer survivorship: the role of rehabilitation according to the International Classification of Functioning, Disability and Health-a scoping review. Curr Oncol Rep. 2022;24(9):1163-75.

14. Sheppard DM, O'Connor M, Jefford M, Lamb G, Frost D, Ellis N, et al. 'Beyond Cancer' rehabilitation program to support breast cancer survivors to return to health, wellness and work: feasibility study outcomes. Curr Oncol. 2023;30(2):2249-70.

15. Grunfeld E, Earle CC. The interface between primary and oncology specialty care: treatment through survivorship. J Natl Cancer Inst Monogr. 2010;2010(40):25-30.

16. Pimentel-Parra GA, García-Vivar C, Escalada-Hernández P, San Martín-Rodríguez L, Soto-Ruiz N. Systematic review of clinical practice guidelines for long-term breast cancer survivorship: assessment of quality and evidence-based recommendations. Br J Cancer. 2025;133:178-93.

17. Runowicz CD, Leach CR, Henry NL, Henry KS, Mackey HT, Cowens-Alvarado RL, et al. American Cancer Society/American Society of Clinical Oncology breast cancer survivorship care guideline. CA Cancer J Clin. 2016;66(1):43-73.

18. World Health Organization. Package of interventions for rehabilitation: module 7, malignant neoplasm [Internet]. Geneva: WHO; 2023 [cited 2026 Mar 9]. Available from: https://www.who.int/publications/i/item/9789240071254

19. Ong WL, Schouwenburg MG, van Bommel ACM, Stowell C, Allison KH, Benn KE, et al. A standard set of value-based patient-centered outcomes for breast cancer: the International Consortium for Health Outcomes Measurement (ICHOM) initiative. JAMA Oncol. 2017;3(5):677-85.

20. Ebbestad FE, Ammitzbøll G, Horsbøll TA, Andersen I, Johansen C, Zehran B, et al. The long-term burden of a symptom cluster and association with longitudinal physical and emotional functioning in breast cancer survivors. Acta Oncol. 2023;62(7):706-13.

21. Cormier JN, Xing Y, Zaniletti I, Askew RL, Stewart BR, Armer JM. Minimal limb volume change has a significant impact on breast cancer survivors. Lymphology. 2009;42(4):161-75.

22. Stout NL, Binkley JM, Schmitz KH, Andrews K, Hayes SC, Campbell KL, et al. A prospective surveillance model for rehabilitation for women with breast cancer. Cancer. 2012;118(8 Suppl):2191-200.

23. Lee TS, Kilbreath SL, Refshauge KM, Herbert RD, Beith JM. Prognosis of the upper limb following surgery and radiation for breast cancer. Breast Cancer Res Treat. 2008;110(1):19-37.

24. Rietman JS, Dijkstra PU, Hoekstra HJ, Eisma WH, Szabo BG, Groothoff JW, et al. Late morbidity after treatment of breast cancer in relation to daily activities and quality of life: a systematic review. Eur J Surg Oncol. 2003;29(3):229-38.

25. Skjødt Rafn B, Jensen S, Bjerre ED, Wittenkamp MC, Benjaminsen K, Christensen LP, et al. Prospective surveillance for breast cancer-related lymphedema (PROTECT). Acta Oncol. 2023;62(7):808-13.

26. Anbari AB, Wanchai A, Armer JM. Breast cancer-related lymphedema and quality of life: a qualitative analysis over years of survivorship. Chronic Illn. 2021;17(3):257-68.

27. Ebaugh D, Spinelli B, Schmitz KH. Shoulder impairments and their association with symptomatic rotator cuff disease in breast cancer survivors. Med Hypotheses. 2011;77(4):481-7.

28. Horowitz EH, Aibinder WR. Shoulder impingement syndrome. Phys Med Rehabil Clin N Am. 2023;34(2):311-34.

29. Diercks R, Bron C, Dorrestijn O, Meskers C, Naber R, de Ruiter T, et al. Guideline for diagnosis and treatment of subacromial pain syndrome: a multidisciplinary review by the Dutch Orthopaedic Association. Acta Orthop. 2014;85(3):314-22.

30. Witten A, Mikkelsen K, Wagenblast Mayntzhusen T, Clausen MB, Thorborg K, Hölmich P, et al. Terminology and diagnostic criteria used in studies investigating patients with subacromial pain syndrome from 1972 to 2019: a scoping review. Br J Sports Med. 2023;57(13):864-71.

31. Michener LA, McClure PW, Karduna AR. Anatomical and biomechanical mechanisms of subacromial impingement syndrome. Clin Biomech. 2003;18(5):369-79.

32. Lang AE, Dickerson CR, Kim SY, Stobart J, Milosavljevic S. Impingement pain affects kinematics of breast cancer survivors in work-related functional tasks. Clin Biomech. 2019;70:223-30.

33. Kalichman L, Menahem I, Treger I. Myofascial component of cancer pain: review. J Bodyw Mov Ther. 2019;23(2):311-5.

34. Rezende MS, Rossi DM, Ribeiro de Lima AM, Clemente GS, Siriani de Oliveira A, Caldeira de Oliveira Guirro E. Shoulder and scapulothoracic impairments in women with breast cancer-related lymphedema in the upper limb: a cross-sectional study. J Bodyw Mov Ther. 2024;37:177-82.

35. Nesvold IL, Fossa SD, Holm I, Naume B, Dahl AA. Arm/shoulder problems in breast cancer survivors are associated with reduced health and poorer physical quality of life. Acta Oncol. 2010;49(3):347-53.

36. Jeong HJ, Sim YJ, Hwang KH, Kim GC. Causes of shoulder pain in women with breast cancer-related lymphedema: a pilot study. Yonsei Med J. 2011;52(4):661-7.

37. Ryans K, Perdomo M, Davies CC, Levenhagen K, Gilchrist L. Rehabilitation interventions for the management of breast cancer-related lymphedema: developing a patient-centered, evidence-based plan of care throughout survivorship. J Cancer Surviv. 2023;17(1):237-45.

38. Stubblefield MD, Keole N. Upper body pain and functional disorders in patients with breast cancer. PM R. 2014;6(2):170-83.

39. Yang S, Park DH, Ahn SH, Kim J, Lee JW, Han JY, et al. Prevalence and risk factors of adhesive capsulitis of the shoulder after breast cancer treatment. Support Care Cancer. 2017;25(4):1317-22.

40. Gala-Alarcón P, Prieto-Gómez V, Bailón-Cerezo J, Yuste-Sánchez MJ, Arranz-Martín B, Torres-Lacomba M. Changes in shoulder outcomes using ultrasonographic assessment of breast cancer survivors: a prospective longitudinal study with 6-month follow-up. Sci Rep. 2021;11(1):23016.

41. Kim TH, Adamson SR, Lim P, Tran K, Nguyen K, Neoh D, et al. Prevalence and quality of life in patients with lymphoedema following axillary clearance for breast and cutaneous malignancies. Lymphatics. 2024;2(3):133-46.

42. Földi M. On the pathophysiology of arm lymphedema after treatment for breast cancer. Lymphology. 1995;28(3):151-8.

43. Levenhagen K, Davies C, Perdomo M, Ryans K, Gilchrist L. Diagnosis of upper-quadrant lymphedema secondary to cancer: clinical practice guideline from the Oncology Section of APTA. Rehabil Oncol. 2017;35(3):E1-18.

44. Gençay Can A, Ekşioğlu E, Çakçı FA. Early detection and treatment of subclinical lymphedema in patients with breast cancer. Lymphat Res Biol. 2019;17(3):368-73.

45. DiSipio T, Rye S, Newman B, Hayes S. Incidence of unilateral arm lymphoedema after breast cancer: a systematic review and meta-analysis. Lancet Oncol. 2013;14(6):500-15.

46. Torgbenu E, Luckett T, Buhagiar MA, Chang S, Phillips JL. Prevalence and incidence of cancer-related lymphedema in low- and middle-income countries: a systematic review and meta-analysis. BMC Cancer. 2020;20(1):604.

47. Levenhagen K, Davies C, Perdomo M, Ryans K, Gilchrist L. Diagnosis of upper quadrant lymphedema secondary to cancer: clinical practice guideline from the Oncology Section of the American Physical Therapy Association. Phys Ther. 2017;97(7):729-45.

48. Boyages J, Vicini FA, Shah C, Koelmeyer LA, Nelms JA, Ridner SH. The risk of subclinical breast cancer-related lymphedema by the extent of axillary surgery and regional node irradiation: a randomized controlled trial. Int J Radiat Oncol Biol Phys. 2021;109(4):987-97.

49. De Vrieze T, Nevelsteen I, Thomis S, De Groef A, Tjalma WAA, Gebruers N, et al. What are the economic burden and costs associated with the treatment of breast cancer-related lymphoedema? A systematic review. Support Care Cancer. 2020;28(2):439-49.

50. Ridner SH, Montgomery LD, Hepworth JT, Stewart BR, Armer JM. Comparison of upper limb volume measurement techniques and arm symptoms between healthy volunteers and individuals with known lymphedema. Lymphology. 2007;40(1):35-46.

51. Stout Gergich NL, Pfalzer LA, McGarvey C, Springer B, Gerber LH, Soballe P. Preoperative assessment enables the early diagnosis and successful treatment of lymphedema. Cancer. 2008;112(12):2809-19.

52. Czerniec SA, Ward LC, Refshauge KM, Beith J, Lee MJ, York S, et al. Assessment of breast cancer-related arm lymphedema: comparison of physical measurement methods and self-report. Cancer Invest. 2010;28(1):54-62.

53. Pappalardo M, Starnoni M, Franceschini G, Baccarani A, De Santis G. Breast cancer-related lymphedema: recent updates on diagnosis, severity and available treatments. J Pers Med. 2021;11(5):402.

54. Paskett ED, Dean JA, Oliveri JM, Harrop JP. Cancer-related lymphedema risk factors, diagnosis, treatment, and impact: a review. J Clin Oncol. 2012;30(30):3726-33.

55. Taylor R, Jayasinghe UW, Koelmeyer L, Ung O, Boyages J. Reliability and validity of arm volume measurements for assessment of lymphedema. Phys Ther. 2006;86(2):205-14.

56. Choi YH, Seo KS. Correlation among bioimpedance analysis, sonographic and circumferential measurement in assessment of breast cancer-related arm lymphedema. Lymphology. 2014;47(3):123-33.

57. Michelotti A, Invernizzi M, Lopez G, Lorenzini D, Nesa F, De Sire A, et al. Tackling the diversity of breast cancer-related lymphedema: perspectives on diagnosis, risk assessment, and clinical management. Breast. 2019;44:15-23.

58. Özçakar L, Kara M, Chang KV, Çarl AB, Akkaya N, Tok F, et al. Nineteen reasons why physiatrists should do musculoskeletal ultrasound: EURO-MUSCULUS/USPRM recommendations. Am J Phys Med Rehabil. 2015;94(6):e45-9.

59. Suehiro K, Yamamoto S, Honda S, Morikage N, Harada E, Takemoto Y, et al. Perioperative variations in indices derived from noninvasive assessments to detect postmastectomy lymphedema. J Vasc Surg Venous Lymphat Disord. 2019;7(4):562-9.

60. Suehiro K, Morikage N, Murakami M, Yamashita O, Samura M, Hamano K. Significance of ultrasound examination of skin and subcutaneous tissue in secondary lower extremity lymphedema. Ann Vasc Dis. 2013;6(2):180-8.

61. Giray E, Yagci I. Diagnostic accuracy of interlimb differences of ultrasonographic subcutaneous tissue thickness measurements in breast cancer-related arm lymphedema. Lymphology. 2019;52(1):1-10.

62. Mellor RH, Bush NL, Stanton AW, Bamber JC, Levick JR, Mortimer PS. Dual-frequency ultrasound examination of skin and subcutis thickness in breast cancer-related lymphedema. Breast J. 2004;10(6):496-503.

63. Ricci V, Ricci C, Gervasoni F, Andreoli A, Özçakar L. From histo-anatomy to sonography in lymphedema: EURO-MUSCULUS/USPRM approach. Eur J Phys Rehabil Med. 2022;58(1):108-17.

64. Yang EJ, Kim SY, Lee WH, Lim JY, Lee J. Diagnostic accuracy of clinical measures considering segmental tissue composition and volume changes of breast cancer-related lymphedema. Lymphat Res Biol. 2018;16(4):368-76.

65. Mander A, Venosi S, Menegatti E, Lee BB, Neuhardt D, Maietti E, et al. Upper limb secondary lymphedema ultrasound mapping and characterization. Int Angiol. 2019;38(4):334-42.

66. Jeon Y, Beom J, Ahn S, Bok SK. Ultrasonographic evaluation of breast cancer-related lymphedema. J Vis Exp. 2017;(119):54709.

67. Park JY, Jeon JY, Cha S. Ultrasonographic features of the skin and subcutis: correlations with the severity of breast cancer-related lymphedema. Ultrasonography. 2024;43(4):284-93.

68. McLaughlin SA, Brunelle CL, Taghian A. Breast cancer-related lymphedema: risk factors, screening, management, and the impact of locoregional treatment. J Clin Oncol. 2020;38(20):2341-50.

69. Smoot BJ, Wong JF, Dodd MJ. Comparison of diagnostic accuracy of clinical measures of breast cancer-related lymphedema: area under the curve. Arch Phys Med Rehabil. 2011;92(4):603-10.

70. Devoogdt N, Pans S, De Groef A, Geraerts I, Christiaens MR, Neven P, et al. Postoperative evolution of thickness and echogenicity of cutis and subcutis of patients with and without breast cancer-related lymphedema. Lymphat Res Biol. 2014;12(1):23-31.

71. Hormes JM, Bryan C, Lytle LA, Gross CR, Ahmed RL, Troxel AB, et al. Impact of lymphedema and arm symptoms on quality of life in breast cancer survivors. Lymphology. 2010;43(1):1-13.

72. Coriddi M, Dayan J, Sobti N, Nash D, Goldberg J, Klassen A, et al. Systematic review of patient-reported outcomes following surgical treatment of lymphedema. Cancers (Basel). 2020;12(3):565.

73. Chima C, Murray B, Moore Z, Costello M, George S. Health-related quality of life and assessment in patients with lower limb lymphoedema: a systematic review. J Wound Care. 2022;31(8):690-9.

74. Alfano CM, Leach CR, Smith TG, Miller KD, Alcaraz KI, Cannady RS, et al. Equitably improving outcomes for cancer survivors and supporting caregivers: a blueprint for care delivery, research, education, and policy. CA Cancer J Clin. 2019;69(1):35-49.

75. Fu MR, Axelrod D, Cleland CM, Qiu Z, Guth AA, Kleinman R, et al. Symptom report in detecting breast cancer-related lymphedema. Breast Cancer (Dove Med Press). 2015;7:345-52.

76. Keeley V, Crooks S, Locke J, Veigas D, Riches K, Hilliam R. A quality of life measure for limb lymphoedema (LYMQoL). J Lymphoedema. 2010;5(1):26-37.

77. Monticone M, Ferriero G, Keeley V, Brunati R, Liquori V, Maggioni S, et al. Lymphedema quality of life questionnaire (LYMQoL): cross-cultural adaptation and validation in Italian women with upper limb lymphedema after breast cancer. Disabil Rehabil. 2022;44(15):4075-80.

78. Uhm KE, Yeo SM, Yoo JS, Hwang JH. Reliability and validity of the Korean version of the Lymphedema Quality of Life Questionnaire in breast cancer-related lymphedema patients. Lymphat Res Biol. 2023;21(2):187-93.

79. Borman P, Yaman A, Denizli M, Karahan S, Özdemir O. The reliability and validity of Lymphedema Quality of Life Questionnaire-Arm in Turkish patients with upper limb lymphedema related to breast cancer. Turk J Phys Med Rehabil. 2018;64(3):205-12.

80. Zhao H, Wu Y, Tao Y, Zhou C, De Vrieze T, Li X, et al. Psychometric validation of the Chinese version of the Lymphedema Functioning, Disability, and Health Questionnaire for upper limb lymphedema in patients with breast cancer-related lymphedema. Cancer Nurs. 2022;45(1):70-82.

81. Schulz T, Warg ML, Heister S, Lidzba K, Ciklatekerlio G, Molter Y, et al. Translation, cross-cultural adaptation and validation of the Lymphedema Quality of Life Questionnaire (LYMQoL) in German-speaking patients with upper limb lymphedema. Healthcare (Basel). 2024;12(18):1881.

82. Liang ZY, Long X, Yang EL, Li YZ, Li ZJ, Xu M, et al. Reliability and validity of the Chinese version of the Lymphedema Quality of Life Questionnaire. Chin Med Sci J. 2021;36(4):295-306.

83. Davies C, Levenhagen K, Ryans K, Perdomo M, Gilchrist L. Interventions for breast cancer-related lymphedema: clinical practice guideline from the Academy of Oncologic Physical Therapy of APTA. Phys Ther. 2020;100(7):1163-79.

84. Wedin M, Fredrikson M, Ahlner E, Falk A, Sandström Å, Lindahl G, et al. Validation of the Lymphoedema Quality of Life Questionnaire (LYMQoL) in Swedish cancer patients. Acta Oncol. 2020;59(3):365-71.

85. International Society of Lymphology Executive Committee. The diagnosis and treatment of peripheral lymphedema: 2020 consensus document of the International Society of Lymphology. Lymphology. 2020;53(1):3-19.

86. Klarić-Kukuz I, Mršić DB, Matana A, Barun B, Aljinović J, Marinović-Guić M, et al. High-frequency ultrasonography imaging: anatomical measuring site as potential clinical marker for early identification of breast cancer-related lymphedema. Biomedicines. 2025;13(6):1396.

87. Armer JM, Stewart BR. A comparison of four diagnostic criteria for lymphedema in a post-breast cancer population. Lymphat Res Biol. 2005;3(4):208-17.

88. Soran A, Ozmen T, McGuire KP, Diego EJ, McAuliffe PF, Bonaventura M, et al. The importance of detection of subclinical lymphedema for the prevention of breast cancer-related clinical lymphedema after axillary lymph node dissection: a prospective observational study. Lymphat Res Biol. 2014;12(4):289-94.

89. Bundred N, Foden P, Todd C, Morris J, Watterson D, Purushotham A, et al. Increases in arm volume predict lymphoedema and quality of life deficits after axillary surgery: a prospective cohort study. Br J Cancer. 2020;123(1):17-25.

90. Brunelle CL, Roberts SA, Horick NK, Gillespie TC, Jacobs JM, Daniell KM, et al. Integrating symptoms into the diagnostic criteria for breast cancer-related lymphedema: applying results from a prospective surveillance program. Phys Ther. 2020;100(12):2186-97.

91. Klarić-Kukuz I, Ćurković A, Grančić J, Aljinović J, Barun B, Pivalica D, et al. Measuring what matters for breast cancer survivors: translation, cross-cultural adaptation and validation of the Croatian version of Lymphedema Quality of Life Tool-Arm. J Clin Med. 2026;15(2):465.

92. Selame LAJ, Matsas B, Krauss B, Goldsmith AJ, Shokoohi H. A stepwise guide to performing shoulder ultrasound: the acromio-clavicular joint, biceps, subscapularis, impingement, supraspinatus protocol. Cureus. 2021;13(9):e18354.

93. Klarić-Kukuz I, Aljinović J, Barun B, Roki M, Benzon B, Budimir Mršić D, et al. Subacromial pain syndrome in breast cancer survivors: are structural shoulder changes verified by ultrasound clinically relevant? Diagnostics (Basel). 2025;15(1):70.

94. Tassenoy A, De Mey J, De Ridder F, Van Schuerbeeck P, Vanderhasselt T, Lamote J, et al. Postmastectomy lymphoedema: different patterns of fluid distribution visualised by ultrasound imaging compared with magnetic resonance imaging. Physiotherapy. 2011;97(3):234-43.

95. Deltombe T, Jamart J, Recloux S, Legrand C, Vandenbroeck N, Theys S, et al. Reliability and limits of agreement of circumferential, water displacement, and optoelectronic volumetry in the measurement of upper limb lymphedema. Lymphology. 2007;40(1):26-34.

96. Jureša V, Ivanković D, Vuletić G, Babić-Banaszak A, Srček I, Mastilica M, et al. The Croatian Health Survey-SF-36: I. General quality of life assessment. Coll Antropol. 2000;24(1):69-78.

97. Maslić Seršić D, Vuletić G. Psychometric evaluation and establishing norms of Croatian SF-36 health survey: framework for subjective health research. Croat Med J. 2006;47(1):95-102.

98. Farrar JT, Young JP Jr, LaMoreaux L, Werth JL, Poole RM. Clinical importance of changes in chronic pain intensity measured on an 11-point numerical pain rating scale. Pain. 2001;94(2):149-58.

99. Binkley JM, Harris SR, Levangie PK, Pearl M, Guglielmino J, Kraus V, et al. Patient perspectives on breast cancer treatment side effects and the prospective surveillance model for physical rehabilitation for women with breast cancer. Cancer. 2012;118(8 Suppl):2207-16.

100. Moosmayer S, Smith HJ, Tariq R, Larmo A. Prevalence and characteristics of asymptomatic tears of the rotator cuff: an ultrasonographic and clinical study. J Bone Joint Surg Br. 2009;91(2):196-200.

101. Yamaguchi K, Tetro AM, Blam O, Evanoff BA, Teefey SA, Middleton WD. Natural history of asymptomatic rotator cuff tears: a longitudinal analysis of asymptomatic tears detected sonographically. J Shoulder Elbow Surg. 2001;10(3):199-203.

102. Kim JH, Kim SH, Kim HR, Lee SH, Yoon SY, Yang JH, et al. Ultrasonographic evaluation of chronic shoulder pain after breast cancer surgery: single-center cross-sectional study. Sci Rep. 2020;10(1):16792.

103. Khoschnau S, Milosavjevic J, Sahlstedt B, Rylance R, Rahme H, Kadum B. High prevalence of rotator cuff tears in a population who never sought care for shoulder problems: a clinical, ultrasonographic and radiographic screening study. Eur J Orthop Surg Traumatol. 2020;30(3):457-63.

104. Penn IW, Chang YC, Chuang E, Chen CM, Chung CF, Kuo CY, et al. Risk factors and prediction model for persistent breast cancer-related lymphedema: a 5-year cohort study. Support Care Cancer. 2019;27(3):991-1000.

105. Sagen A, Kaaresen R, Sandvik L, Thune I, Risberg MA. Upper limb physical function and adverse effects after breast cancer surgery: a prospective 2.5-year follow-up study and preoperative measures. Arch Phys Med Rehabil. 2014;95(5):875-81.

106. Adriaenssens N, Belsack D, Buyl R, Ruggiero L, Breucq C, De Mey J, et al. Ultrasound elastography as an objective diagnostic measurement tool for lymphoedema of the treated breast in breast cancer patients following breast-conserving surgery and radiotherapy. Radiol Oncol. 2012;46(4):284-95.

107. Mafu TS, September AV, Shamley D. The potential role of angiogenesis in the development of shoulder pain, shoulder dysfunction, and lymphedema after breast cancer treatment. Cancer Manag Res. 2018;10:81-90.

108. Stout NL, Pfalzer LA, Levy E, McGarvey C, Springer B, Gerber LH, et al. Segmental limb volume change as a predictor of the onset of lymphedema in women with early breast cancer. PM R. 2011;3(12):1098-105.

109. Friedman R, Lee C, Kinney JR, Salehi BP, Kim G, Singhal D, et al. Fluid distribution patterns in early-stage upper extremity lymphedema. Ann Plast Surg. 2023;90(6 Suppl 5):S622-5.

110. Zhang X, Oliveri JM, Paskett ED. Features, predictors, and treatment of breast cancer-related lymphedema. Curr Breast Cancer Rep. 2020;12(4):244-54.

111. Stanton AW, Badger C, Sitzia J. Non-invasive assessment of the lymphedematous limb. Lymphology. 2000;33(3):122-35.

112. Johnson KC, DeSarno M, Ashikaga T, Dee J, Henry SM. Ultrasound and clinical measures for lymphedema. Lymphat Res Biol. 2016;14(1):8-17.

113. Specht MC, Miller CL, Russell TA, Horick N, Skolny MN, O'Toole JA, et al. Defining a threshold for intervention in breast cancer-related lymphedema: what level of arm volume increase predicts progression? Breast Cancer Res Treat. 2013;140(3):485-94.

114. de Rezende LF, Piloni JPM, Kempa VL, Silva JFR, Vilas Boas VF, Carvalho RL, et al. Ultrasonography as an instrument to evaluate lymphedema secondary to breast cancer: systematic review. J Vasc Bras. 2023;22:e20220144.

115. Cornish BH, Chapman M, Hirst C, Mirolo B, Bunce IH, Ward LC, et al. Early diagnosis of lymphedema using multiple frequency bioimpedance. Lymphology. 2001;34(1):2-11.

116. Johnson AR, Bravo MG, James TA, Suami H, Lee BT, Singhal D. The all but forgotten Mascagni-Sappey pathway: learning from immediate lymphatic reconstruction. J Reconstr Microsurg. 2020;36(1):28-31.

117. Polat AV, Ozturk M, Polat AK, Karabacak U, Bekci T, Murat N. Efficacy of ultrasound and shear wave elastography for the diagnosis of breast cancer-related lymphedema. J Ultrasound Med. 2020;39(4):795-803.

118. Kim SY, Lee CH, Heo SJ, Moon MH. The clinical usefulness of lymphedema measurement technique using ultrasound. Lymphat Res Biol. 2021;19(4):340-6.

119. Suehiro K, Morikage N, Yamashita O, Harada T, Samura M, Takeuchi Y, et al. Skin and subcutaneous tissue ultrasonography features in breast cancer-related lymphedema. Ann Vasc Dis. 2016;9(4):312-6.

120. Meilani E, Zanudin A, Mohd Nordin NA. Psychometric properties of quality of life questionnaires for patients with breast cancer-related lymphedema: a systematic review. Int J Environ Res Public Health. 2022;19(5):2519.

121. Grünherz L, Hulla H, Uyulmaz S, Giovanoli P, Lindenblatt N. Patient-reported outcomes following lymph reconstructive surgery in lower limb lymphedema: a systematic review of the literature. J Vasc Surg Venous Lymphat Disord. 2021;9(3):811-9.e2.

122. van de Pas CB, Biemans AA, Boonen RS, Viehoff PB, Neumann HA. Validation of the Lymphoedema Quality-of-Life Questionnaire (LYMQoL) in Dutch patients diagnosed with lymphoedema of the lower limbs. Phlebology. 2016;31(4):257-63.

123. Pusic A, Liu JC, Chen CM, Cano S, Davidge K, Klassen A, et al. A systematic review of patient-reported outcome measures in head and neck cancer surgery. Otolaryngol Head Neck Surg. 2007;136(4):525-35.

124. Teo I, Novy DM, Chang DW, Cox MG, Fingeret MC. Examining pain, body image, and depressive symptoms in patients with lymphedema secondary to breast cancer. Psychooncology. 2015;24(11):1377-83.

125. Bulley C, Gaal S, Coutts F, Blyth C, Jack W, Chetty U, et al. Comparison of breast cancer-related lymphedema (upper limb swelling) prevalence estimated using objective and subjective criteria and relationship with quality of life. Biomed Res Int. 2013;2013:807569.

8. SAŽETAK

Naslov:

Značaj radioloških i kliničkih obilježja pacijentica s rakom dojke liječenih u dnevnoj bolnici za limfedem

Cilj:

Cilj ove doktorske disertacije bio je procijeniti vrijednost ultrazvučne dijagnostike u otkrivanju strukturnih mišićno-koštanih promjena ramena i ranih oblika limfedema gornjeg ekstremiteta kod žena nakon liječenja raka dojke te validirati hrvatsku verziju specifičnog upitnika za procjenu kvalitete života žena s limfedemom gornjeg ekstremiteta (LYMQoL-UL-CRO). Dodatni cilj bio je ispitati povezanost objektivnih ultrazvučnih nalaza s prisutnošću boli, kliničkim obilježjima limfedema i subjektivnim ishodima kvalitete života.

Metode:

Doktorska disertacija temelji se na tri presječna istraživanja provedena u populaciji žena koje su preživjele rak dojke. U prvom istraživanju analizirana je i vrsta ultrazvučno potvrđenih strukturnih promjena ramena te njihova povezanost s boli u ramenu. U drugom istraživanju ispitana je dijagnostička vrijednost ultrazvučnih mjerenja debljine kože i potkožja u detekciji limfedema gornjeg ekstremiteta, uključujući rane stadije definirane minimalnim povećanjem volumena ruke. Treće istraživanje obuhvatilo je prijevod, kulturološku prilagodbu i psihometrijsku validaciju hrvatske verzije upitnika LYMQoL-UL-CRO te analizu povezanosti kvalitete života s kliničkim obilježjima limfedema. Primijenjene su odgovarajuće deskriptivne i inferencijalne statističke metode, uključujući multivarijantne regresijske analize.

Rezultati:

Ultrazvučno potvrđene strukturne promjene ramena bile su vrlo česte u populaciji žena koje su preživjele rak dojke, pri čemu su najčešće zahvaćene tetive rotatorne manšete, osobito supraspinatusna tetiva. Patološki nalazi nisu bili ograničeni isključivo na operiranu stranu. U više od 90 % bolnih ramena identificirane su strukturne promjene, što potvrđuje kliničku vrijednost ultrazvuka u evaluaciji boli u ramenu.

Ultrazvučno mjerena debljina kože, osobito u području srednje nadlaktice, pokazala se snažno povezanom s prisutnošću i težinom limfedema, uključujući rane stadije bolesti prije pojave

klinički vidljive otekline. Ultrazvuk je omogućio detekciju subkliničkih promjena koje nisu bile prepoznatljive konvencionalnim volumskim i cirkumferencijskim metodama.

Hrvatska verzija upitnika LYMQoL-UL-CRO pokazala je vrlo dobra psihometrijska svojstva. Lošiji ishodi kvalitete života bili su prisutni i kod žena s minimalnim promjenama volumena ruke, što upućuje na to da subjektivni teret bolesti ne ovisi isključivo o objektivnim kliničkim pokazateljima.

Zaključak:

Rezultati ove doktorske disertacije potvrđuju da dugoročne posljedice liječenja raka dojke uključuju međusobno povezane mišićno-koštane, limfne i psihosocijalne promjene koje značajno utječu na funkcioniranje i kvalitetu života žena koje su preživjele rak dojke. Ultrazvučna dijagnostika predstavlja vrijedan, neinvazivan i objektivan alat za ranu detekciju strukturnih promjena ramena i limfedema, dok validirani upitnik LYMQoL-UL-CRO omogućuje cjelovitu procjenu subjektivnog tereta bolesti. Integracija objektivnih slikovnih metoda i pacijentima prijavljenih ishoda pruža temelj za razvoj personaliziranih, dugoročnih rehabilitacijskih i praćenih strategija u skrbi za žene nakon liječenja raka dojke.

Ključne riječi: rak dojke; preživjele od raka dojke; bol u ramenu; subakromijalni bolni sindrom; ultrazvučna dijagnostika; rotatorna manšeta; limfedem gornjeg ekstremiteta; debljina kože; kvaliteta života; LYMQoL-UL-CRO

9. SUMMARY

Title:

The Significance of Radiological and Clinical Features in Breast Cancer Patients Treated in a Lymphedema Day Hospital

Objective:

The aim of this doctoral dissertation was to evaluate the value of ultrasound imaging in detecting structural musculoskeletal shoulder changes and early stages of upper limb lymphedema in breast cancer survivors, and to validate the Croatian version of the Lymphedema Quality of Life Questionnaire–Upper Limb (LYMQoL-UL-CRO). An additional objective was to examine the relationship between objective ultrasound findings, shoulder pain, clinical characteristics of lymphedema, and patient-reported quality of life outcomes.

Methods:

This doctoral dissertation is based on three cross-sectional studies conducted in a population of breast cancer survivors. The first study assessed the prevalence and type of ultrasound-confirmed structural shoulder abnormalities and their association with shoulder pain. The second study evaluated the diagnostic value of ultrasound measurements of skin and subcutaneous tissue thickness in detecting upper limb lymphedema, including early stages defined by minimal arm volume increase. The third study involved translation, cultural adaptation, and psychometric validation of the Croatian version of the LYMQoL-UL questionnaire, as well as analysis of associations between quality of life outcomes and clinical characteristics of lymphedema. Appropriate descriptive and inferential statistical analyses, including multivariable regression models, were applied.

Results:

Ultrasound-confirmed structural shoulder abnormalities were highly prevalent among breast cancer survivors, with rotator cuff tendons, particularly the supraspinatus tendon being most frequently affected. Pathological findings were not limited to the operated side. Structural abnormalities were identified in more than 90 % of painful shoulders, supporting the clinical value of ultrasound in shoulder pain evaluation.

Ultrasound-measured skin thickness, particularly in the mid-upper arm region, showed a strong association with the presence and severity of lymphedema, including early stages prior to clinically visible swelling. Ultrasound enabled detection of subclinical tissue changes that were not identifiable using conventional volume or circumference measurements.

The Croatian version of the LYMQoL-UL-CRO demonstrated very good psychometric properties. Impaired quality of life was observed even in women with minimal arm volume changes, indicating that subjective disease burden is not solely dependent on objective clinical measures.

Conclusion:

The findings of this doctoral dissertation demonstrate that long-term consequences of breast cancer treatment encompass interconnected musculoskeletal, lymphatic, and psychosocial impairments that substantially affect function and quality of life in breast cancer survivors. Ultrasound imaging represents a valuable, non-invasive, and objective tool for early detection of shoulder pathology and lymphedema, while the validated LYMQoL-UL-CRO questionnaire enables comprehensive assessment of patient-reported disease burden. Integrating objective imaging findings with patient-reported outcomes provides a foundation for the development of personalized, long-term surveillance and rehabilitation strategies in breast cancer survivorship care.

Keywords: breast cancer; breast cancer survivors; shoulder pain; subacromial pain syndrome; ultrasound imaging; rotator cuff; upper limb lymphedema; skin thickness; quality of life; LYMQoL-UL-CRO

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Izvorni znanstveni i pregledni radovi

- Burger, Ante; Bjelanović, Luka; Klarić-Kukuz, Ivana. Ozljede u kontaktnim timskim sportovima i primjeri modificiranih igara za primjenu u nastavi i školskom sportu // Hrvatski časopis zdravstvenih znanosti, 1 (2021), 2; 87-93.
- Klarić Kukuz, Ivana; Grančić, Josipa; Pavlović, Marta; Barić Žižić, Ana; Aljinović, Jure; Marinović, Ivanka; Poljičanin, Ana. A Case Report of Late Onset Primary Lymphedema - From Diagnosis to Successful Management Strategies Case study // Hrvatski časopis zdravstvenih znanosti (2022) (domaća recenzija, prihvaćen)
- Grančić, Josipa; Klarić Kukuz, Ivana; Vlak, Tonko; Aljinović, Jure; Marinović, Ivanka; Poljičanin, Ana. Pregled sistematskih preglednih članaka o utjecaju vježbi na smanjenje

limfedema kod žena operiranih od karcinoma dojke // Fizikalna i rehabilitacijska medicina (2022) (domaća recenzija, prihvaćen)

- Klarić-Kukuz, I.; Aljinović, J.; Barun, B.; Roki, M.; Benzon, B.; Budimir Mršić, D.; Marinović Guić, M.; Poljičanin, A. Subacromial Pain Syndrome in Breast Cancer Survivors-Are Structural Shoulder Changes Verified by Ultrasound Clinically Relevant? Diagnostics 2025, 15, 70. https://doi.org/10.3390/diagnostics15010070.
- Klarić-Kukuz, I.; Mršić, D.B.; Matana, A.; Barun, B.; Aljinović, J.; Marinović-Guić, M.; Poljičanin, A. High-Frequency Ultrasonography Imaging: Anatomical Measuring Site as Potential Clinical Marker for Early Identification of Breast Cancer-Related Lymphedema. Biomedicines2025. 1396. https://doi.org/10.3390/biomedicines13061396.
- Klarić-Kukuz I, Ćurković A, Grančić J, Aljinović J, Barun B, Pivalica D, Poljičanin A. Measuring What Matters for Breast Cancer Survivors: Translation, Cross-Cultural Adaptation and Validation of the Croatian Version of Lymphedema Quality of Life Tool-Arm. J Clin Med. 2026 Jan 7;15(2):465. doi: 10.3390/jcm15020465. PMID: 41598404; PMCID: PMC12842119.

Poglavlja u knjizi

- Poljičanin, Ana; Klarić Kukuz, Ivana, Grančić, Josipa. Limfedem // Akutne i kronične rane, od teorije do prakse / Huljev, Dubravko ; Žulec, Mirna (ur.). Bjelovar: Kalida, 2021. str. 145-178
- Marinović M, Aljinović A, Poljičanin A, Barun B, Parlov I, Klarić Kukuz M. Funkcionalna anatomija lokomotornog sustava. Split: Sveučilište u Splitu, Fakultet zdravstvenih studija; 2019.
- Klarić-Kukuz I. Prehabilitacija - kako uspješno prevenirati komplikacije operativnog zahvata karcinoma dojke? Split: Sveučilišni odjel zdravstvenih studija Sveučilišta u Splitu; 2023.

Kongresna priopćenja

- Klarić-Kukuz, Ivana; Košević, Tamara; Aljinović, Jure; Marinović, Ivanka; Poljičanin, An Initiative for the establishment of the National Lymphoedema Framework Croatia // Pprogramme & Abstracts. Kopenhagen: ILF: DSFS, 2021. str. 133-134 (poster, međunarodna recenzija, sažetak, ostalo)
- Klarić Kukuz, Ivana; Pavlović, Marta; Grančić, Josipa; Aljinović, Jure; Marinović, Ivanka; Poljičanin, Ana. Chronic Primary Lymphedema - Proper Physiotherapy Treatment Management Can Make a Difference // 9. hrvatski kongres fizikalne i rehabilitacijske medicine s međunarodnim sudjelovanjem / Vlak, Tonko ; Grubišić, Frane ; Aljinović, Jure ; (ur.). Zagreb: Printera, 2022. str. 112-112 (poster, domaća recenzija, sažetak, stručni)
- Poljičanin, Ana; Klarić Kukuz, Ivana; Grančić, Josipa; Pavlović, Marta; Marinović, Ivanka; Aljinović, Jure Primary lymphedema – Do we have strategies to avoid late diagnosis? – Case report // Fizikalna i rehabilitacijska medicina - Knjiga sažetaka / Vlak, Tonko, Grubišić, Frane, Aljinović, Jure (ur.).
- Zagreb: Printera, 2022. str. 127-127 (poster, domaća recenzija, sažetak, stručni)
- Poljičanin, A., Klarić-Kukuz, I., Aljinović, J., Barun, B., Stipić, M., Marinović Guić, M,. Košta, V. (2024). ELEPHANTIASIS NEUROMATOSA - RIJETKA I EKSTREMNA MANIFESTACIJA PLEKSIFORMNOG NEUROFIBROMA U BOLESNIKA S NEUROFIBROMATOZOM TIPA 1 DIJAGNOSTICIRANA U RANOJ FAZI. Fizikalna i rehabilitacijska medicina, 38 (1-2), 152-153. https://doi.org/10.21751/FRM-38-1-2-66
- Roki, M., Klarić-Kukuz, I., Barun, B., Aljinović, J., Živalj, A., Mateljak, M., Poljičanin, A. (2024). INCIDENTAL ULTRASOUND FINDING OF BILATERAL DEFICIENCY OF THE PECTORALIS MAJOR MUSCLE IN BREAST CANCER SURVIVOR – COULD IT BE POLAND SYNDROME? A CASE REPORT. Fizikalna i rehabilitacijska medicina, 38 (1-2), 158-159. https://doi.org/10.21751/FRM-38-1-2-69
- Klarić-Kukuz, I, Aljinović, J, Barun, B, Roki, M, Pivalica, D, Poljičanin A. (2025.) Beyond the Swelling: Exploring Neuropathic Pain in Breast Cancer Survivors with Lymphedema Assesment and clinical implication Fizikalna i rehabilitacijska medicina, 38 (1-2)

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11. RADOVI OBJAVLJENI U DOKTORSKOJ DISERTACIJI

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Article

Subacromial Pain Syndrome in Breast Cancer Survivors—Are Structural Shoulder Changes Verified by Ultrasound Clinically Relevant?

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Abstract: Background/Objectives: Shoulder pain is a common treatment outcome in breast cancer survivors. While various risk factors and mechanisms for shoulder pain have been proposed, evidence is inconsistent. Increased risk of subacromial pain syndrome exists, which can lead to disability and reduced quality of life if untreated. Ultrasound is a valuable tool for detecting rotator cuff changes aiding in timely diagnosis of subacromial pain syndrome. This study aimed to assess the prevalence of rotator cuff changes to better understand chronic shoulder pain in breast cancer survivors. **Methods**: This cross-sectional study included 74 breast cancer survivors from the University Hospital Split. Data were collected via questionnaires and clinical interviews. Bilateral shoulder ultrasounds were performed by two blinded investigators. Categorical variables were analyzed using Chi-squared tests, and continuous variables were analyzed with T-tests or Mann–Whitney tests. **Results**: Pathological findings were similarly prevalent on the operated and non-operated sides ($p = 0.3$ and $p = 0.6$). Among participants with shoulder pain, ultrasound-detected pathology was present in 91% of right shoulders and 96% of left shoulders ($p < 0.005$). Non-painful shoulders exhibited pathology in 59% of right and 57% of left shoulders. Ipsilateral pain to the site of breast surgery was reported by 57.7% of participants, with supraspinatus pathology in 56%, acromioclavicular joint pathology in 39%, and subacromial–subdeltoid bursitis in 41%. **Conclusions**: Similar pathology distribution on operated and non-operated sides and frequent asymptomatic findings highlight unresolved causes of shoulder pain in breast cancer survivors. Ultrasound is valuable but requires integration with clinics for accurate diagnosis of the underlying causes of shoulder pain.

Keywords: shoulder pain; rotator cuff; breast neoplasms; diagnostic imaging

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1. Introduction

According to cancer statistics published by the World Health Organization (WHO), breast cancer is the most prevalent cancer among women worldwide and accounts for the highest mortality rate among cancers [1,2]. However, advancements in targeted treatments have led to a steady increase in the number of breast cancer survivors (BCSs) [3]. In high-income countries, the current five-year survival rate for breast cancer has reached approximately 90% [3].

Despite the benefits of targeted breast cancer treatments, these therapies place survivors at risk of developing both short- and long-term structural and functional impairments. Such impairments can result in functional disability and a reduced quality of life [4,5]. Evidence suggests that nearly 90% of breast cancer survivors experience at least one impairment within six months post-treatment, and 62% continue to report impairments six years after completing treatment [6].

Given these findings, raising awareness about the challenges faced by survivors is essential to facilitate timely diagnosis, treatment, and rehabilitation. These considerations emphasize the critical need for multidisciplinary care across the cancer care continuum. This need has also been recognized by the WHO in its 2021 Global Breast Cancer Initiative, which advocates for comprehensive, patient-centered approaches to breast cancer management [7–10].

According to the International Consortium for Health Outcomes Measurement, upper limb dysfunction (ULD) is one of the most prominent treatment outcomes experienced by breast cancer survivors [11]. ULD significantly impacts survivors' ability to perform activities of daily living, often resulting in a loss of independence, reduced capacity to work, and limitations in participating in social activities with family and friends. These challenges collectively contribute to a decreased overall quality of life [12–15].

Commonly reported ipsilateral ULDs vary widely in prevalence: shoulder/arm pain (up to 51%), limited shoulder range of motion (ROM) (up to 50%), decreased arm strength (25%), and lymphedema (6–52%), with prevalence rates depending on the treatment type and population studied [16–21]. Risk factors for ULD development include mastectomy, axillary lymph node dissection (ALND), radiation therapy, and higher body mass index (BMI) [22–25].

Chronic shoulder pain in breast cancer survivors is often attributed to various treatment-related factors [26]. Surgical procedures such as mastectomy and axillary lymph node dissection (ALND) can result in nerve damage, scar tissue formation, and altered shoulder mechanics, all of which contribute to persistent pain [27,28]. Radiation therapy may lead to fibrosis, restricting shoulder mobility and causing further discomfort [27]. Additionally, lymphedema, if present, can impair shoulder function and exacerbate pain [29]. These treatment-related factors often interact, complicating both diagnosis and management of chronic shoulder pain in breast cancer survivors. Therefore, it is crucial to identify the underlying cause of the pain in order to design an appropriate rehabilitation strategy.

Secondary to the above-mentioned treatment-related factors and ULDs, breast cancer survivors are considered at increased risk for developing subacromial pain syndrome, which encompasses various shoulder pathologies. Common conditions include supraspinatus tears (53.3%), biceps tenosynovitis (13.3%), and subdeltoid bursitis (13.3%) [27,30].

Timely diagnosis of subacromial pain syndrome (SAPS) in breast cancer survivors can be effectively facilitated using ultrasound. This imaging technique offers a non-invasive, cost-effective, and reliable method for assessing shoulder pathologies [31]. Ultrasound allows for real-time visualization of soft tissue structures, making it particularly valuable for diagnosing and monitoring the progression of SAPS [31]. Early detection through

ultrasound is critical for guiding appropriate treatment and preventing long-term functional impairment in breast cancer survivors [31].

Although there is speculation in the scientific literature regarding a causative correlation between breast cancer treatment, shoulder pain, and subacromial pain syndrome, imaging studies addressing this topic are scarce, and their findings remain inconclusive [27,28,32–34]. Prevalence of symptomatic or asymptomatic rotator cuff pathology in breast cancer survivors is yet to be determined.

Notably, scarce small sample studies to date have systematically evaluated shoulder pathology and pain in breast cancer survivors [32–34].

To address this gap, the present imaging study was conducted to assess the prevalence of structural bilateral shoulder changes, with the aim of advancing the understanding of chronic shoulder pain in breast cancer survivors.

2. Materials and Methods

2.1. Study Population

This cross-sectional observational study was conducted over a 6-month period from December 2023 to April 2024 on the Lymphedema Clinic breast cancer survivor's cohort at the University Hospital Split, the second largest tertiary healthcare center in Croatia. This study included females aged 18 years and older who had completed treatment for unilateral breast cancer at least 6 months prior to enrollment and had consented to participate. Exclusion criteria included metastatic breast cancer, cognitive disorders, and a history of shoulder surgery. Following the application of exclusion criteria, a total of 74 breast cancer survivors were enrolled in this study (Figure 1).

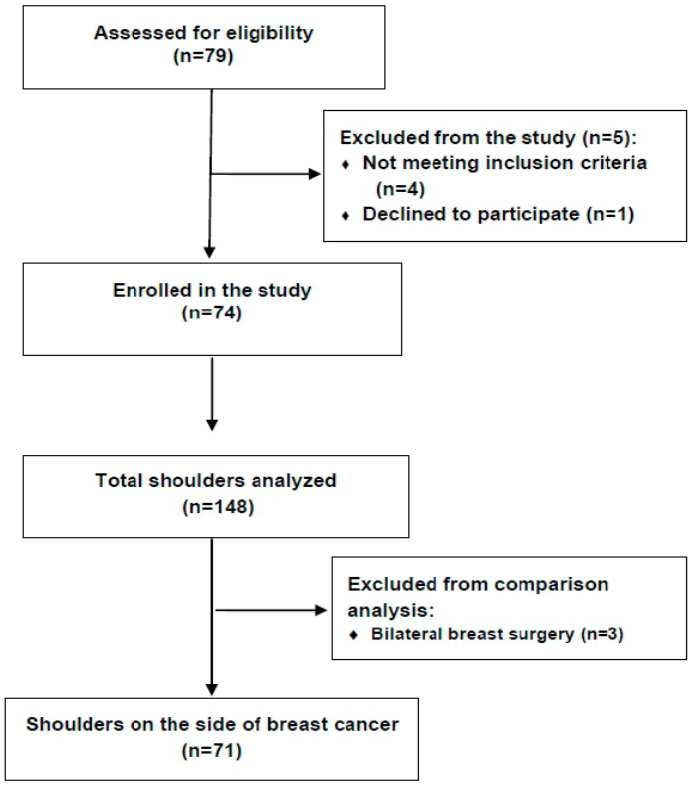

Figure 1. Flowchart of participants enrollment.

This study was approved by the Ethical Committee of the University Hospital Split (protocol code 2181-147/01/06/LJ.Z.-23-2), and informed consent was obtained from all participants prior to enrolment.

2.2. Measurements and Data Collection

Baseline demographic information and comprehensive medical history were collected through self-administered questionnaires and clinical interviews. Missing data, if any, were supplemented by reviewing participants' electronic medical records. Table 1 provides a summary of demographic and disease-related characteristics of the participants.

Table 1. Participants' demographics and disease-related characteristics.

Participants	*n*	%
Age (Median, IQR)	57 (50–64)	100
BMI [1]		
18.5–24.9 kg/m^2	25	33.78
25–29.9 kg/m^2	31	41.89
≥30 kg/m^2	18	24.32
Age at BC [2] diagnosis (Median, IQR)	52 (45–57)	100
Time since BC [2] surgery (Median, IQR)	5 (2–9)	100
Operated side:		
Right	37	50
Left	34	45.95
Both	3	4.05
Type of surgery:		
Mastectomy	47	63.51
Breast-conserving	27	36.49
Breast reconstruction:		
Yes	20	27.02
No	54	72.97
Lymph node removal:		
SLND [3]	27	36.49
ALND [4]	46	62.16
Operation on a dominant side:		
Yes	46	62.16
No	28	37.84
Early postoperative ipsilateral shoulder pain:		
Yes	23	31.08
No	49	66.22
After-surgery complications:		
Yes	54	72.97
No	18	24.32
Radiotherapy:		
Yes	52	70.27
No	22	29.73
Chemotherapy:		
Yes	42	56.80
No	32	43.20
Anti HER2 treatment	12	16.22
Endocrine treatment	53	71.62

Table 1. *Cont.*

Participants	*n*	%
Any shoulder pain at present:		
Yes	46	62.16
No	28	37.84
Self-report of hand swelling:		
Yes	40	54.05
No	34	45.94
Established diagnosis of lymphedema (cm):		
Yes	27	35.06
No	57	74.02

[1] Body mass index, [2] breast cancer, [3] sentinel lymph node dissection, and [4] axillary lymph node dissection.

2.2.1. Arm Circumference Measurement

Circumference measurements were performed by an experienced lymphedema therapist. Participants were seated with their arm resting on an adjustable hydraulic table, flexed at approximately 90° with the forearm pronated. Five measurements were taken at predetermined points starting at the ulnar styloid process of the wrist (designated as point 0), with additional measurements taken every 10 cm along the arm. Measurements were recorded in triplicate at each point using a flexible Juzo tape with 1 mm accuracy, and average values were documented on a standardized form. A patient was considered to have lymphedema if the circumference difference between the arms at any of five measured points was 2 cm or grater [35,36].

2.2.2. Shoulder Ultrasonography

Shoulder ultrasonography was performed by two independent, experienced ultrasound specialists who were blinded to each participant's current pain status and to each other's assessments. Intraobserver variability was assessed using the intraclass correlation coefficient (ICC) for repeated measurements of 10% of shoulders, yielding an ICC of 0.9 (95% CI: 0.85–0.95), indicating excellent agreement. Scans were conducted using a 12 MHz linear probe (General Electrics HealthCare Versana Premier V2, Chicago, Illinois, USA) according to an established protocol [37]. All pathologies were scanned in two perpendicular probe positions. Both shoulders (n = 148) underwent ultrasound examination. The shoulders on the non-operated side served as controls. Three participants with bilateral breast surgery were excluded from the inter-shoulder comparison analysis, resulting in a final sample of 71 participants (Figure 1). The median interval between surgery and shoulder examination was five years (Table 1). The ultrasound images of shoulders were anonymized and independently reviewed, with any pathologies documented. For borderline findings, consensus was reached between the reviewers, and no further imaging was required. All measurements were taken from the coded, scanned images. Pathological findings in the rotator cuff were classified as tendinosis, calcific tendinopathy, and partial/full tears. Acromioclavicular joint (AC) arthrosis was graded from mild to severe. The presence of subacromial-subdeltoid bursitis (SASD), as well as effusion, tenosynovitis, or rupture in the long head of the biceps tendon (LHBT), was also recorded.

2.3. Statistical Analysis

Data were analyzed using Microsoft Office Excel 2016 32-bit (Microsoft Corporation, Redmond, WA, USA). Descriptive statistics were applied, with continuous data presented as medians with interquartile ranges (IQRs), and categorical data were presented as frequen-

cies and percentages. Comparative analyses of categorical variables were conducted using the Chi-squared test, while differences in continuous variables were assessed with either the T-test or Mann–Whitney test, as appropriate. A significance level of $\alpha = 0.05$ ($p < 0.05$) was used for all statistical tests.

3. Results

3.1. The Prevalence of Ultrasound Pathological Findings Identified in Shoulders of Breast Cancer Survivors

In the analysis of all shoulders (n = 148), the most frequently observed pathology was in the supraspinatus tendon (SSP), affecting 45% of all shoulders, followed by acromioclavicular (AC) joint arthrosis, observed in 35% of all shoulders. Pathological findings in the subscapularis (SSC), infraspinatus (ISP), and long head of the biceps tendon (LHBT) were present in 10–15% of all shoulders (Table 2).

Table 2. Bilateral ultrasound pathological findings in shoulders of breast cancer survivors.

Structure	Pathology type	Total (n = 74)				Operated vs. Control Side (n = 71)				Operated vs. Control Side (n = 71)			
		L [1]		R [2]		L [1]-Operated		L [1]-Control		R [2]-Operated		R [2]-Control	
		n = 74	%	n = 74	%	n = 33	%	n = 38	%	n = 38	%	n = 33	%
AC [3] joint	no pathology	52	70.3	45	60.8	20	60.6	29	76.3	25	65.8	17	51.5
	mild arthrosis	12	16.2	15	20.3	8	24.2	4	10.5	7	18.4	8	24.2
	≥moderate arthrosis	10	13.5	14	18.9	5	15.2	5	13.2	6	15.8	8	24.2
LHBT [4]	no pathology	64	86.5	65	87.8	31	93.9	31	81.6	34	89.5	28	84.8
	effusion	7	9.5	6	8.1	2	6.1	4	10.5	1	2.6	5	15.2
	tenosynovitis	2	2.7	3	4.1	0	0.0	2	5.3	3	7.9	0	0.0
	rupture	1	1.4	0	0.0	0	0.0	1	2.6	0	0.0	0	0.0
SSC [5]	no pathology	65	87.8	61	82.4	29	87.9	33	86.8	33	86.8	25	75.8
	partial tear	1	1.4	1	1.4	0	0.0	1	2.6	1	2.6	0	0.0
	full tear	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
	calcification	4	5.4	6	8.1	2	6.1	2	5.3	2	5.3	4	12.1
	tendinosis	4	5.4	6	8.1	2	6.1	2	5.3	2	5.3	4	12.1
SSP [6]	no pathology	41	55.4	40	54.1	19	57.6	21	55.3	18	47.4	20	60.6
	partial tear	7	9.5	12	16.2	1	3.0	4	10.5	9	23.7	2	6.1
	full tear	10	13.5	8	10.8	5	15.2	5	13.2	5	13.2	3	9.1
	calcification	9	12.2	9	12.2	4	12.1	5	13.2	5	13.2	4	12.1
	tendinosis	7	9.5	5	6.8	4	12.1	3	7.9	1	2.6	4	12.1
ISP [7]	no pathology	65	87.8	66	89.2	28	84.8	34	89.5	34	89.5	29	87.9
	partial tear	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
	full tear	1	1.4	1	1.4	0	0.0	1	2.6	1	2.6	0	0.0
	calcification	5	6.8	5	6.8	4	12.1	1	2.6	3	7.9	2	6.1
	tendinosis	3	4.1	2	2.7	1	3.0	2	5.3	0	0.0	2	6.1
SASD [8] bursitis	no	66	89.2	53	71.6	28	84.8	35	92.1	22	57.9	28	84.8
	yes	8	10.8	21	28.4	5	15.2	3	7.9	16	42.1	5	15.2

[1] left (L), [2] right (R), [3] acromioclavicular joint (AC), [4] long head of the biceps tendon (LHBT), [5] subscapularis tendon (SSC), [6] supraspinatus tendon (SSP), [7] infraspinatus tendon (ISP), and [8] subacromial-subdeltoid bursitis (SASD).

The most common specific pathological finding was a tendon tear, with supraspinatus tendon tears identified in 37 shoulders (25%). Of these, 19 (12.8%) were partial tears, and 18 (12.2%) were full-thickness tears. Tears in other rotator cuff tendons were rare, observed in only five shoulders (3.4%) (Table 2).

The second most prevalent pathology was calcific tendinopathy, found in 28 shoulders (18.9%). Calcifications in multiple tendons were present in nine shoulders (6.1%). The SSP tendon was the most frequent site for calcifications (n = 18; 12.2%), followed by the ISP and SSC tendons, each affected in 10 shoulders (6.8%) (Table 2).

Adhesive capsulitis was diagnosed in 3 out of 74 patients, representing approximately 2% of the shoulders analyzed.

The prevalence of pathological ultrasound findings was comparable between right (n = 54, 73%) and left shoulders (n = 53, 72%) (Table 2). No statistically significant differences were identified in the type or frequency of pathologies between the right and left shoulders (p-values ranging from 0.4 to 0.76).

The only statistically significant difference between the right and left shoulders was the prevalence of SASD bursitis, which was present in 28.4% of right shoulders and 10% of left shoulders ($p < 0.001$) (Table 2).

The occurrence of SASD bursitis was not significantly associated with endocrine therapy ($p = 0.427$), chemotherapy ($p = 0.721$), or age ($p = 0.344$).

The prevalence of pathological findings was similar between operated and non-operated shoulders, for both the right and left sides ($p = 0.3$ and $p = 0.6$, respectively) (Table 2).

3.2. Prevalence and Ultrasound Characteristics of Painful Shoulders in Breast Cancer Survivors

At the time of ultrasound examination, 62% of participants reported shoulder pain, either on the operated or non-operated side. Further sub-analysis revealed that 18% reported pain in the left shoulder, 24% in the right shoulder, and 20% in both shoulders. Approximately one-third of patients (38%) reported no shoulder pain (Table 1).

Among patients reporting shoulder pain, ultrasound-detected pathology was present in approximately 90% of cases (91% for the right shoulder and 96% for the left shoulder). In contrast, non-painful shoulders exhibited pathology in 59% of right shoulders and 57% of left shoulders. A statistically significant correlation was confirmed between shoulder pain and pathological findings on ultrasound for both shoulders ($p < 0.005$).

Endocrine therapy was administered to 71.6% of patients, while anti-HER2 treatment was given to 16.2% (Table 1). Endocrine therapy was not associated with an increased prevalence of shoulder pain ($p = 0.60$). Similarly, breast cancer survivors who underwent radiotherapy (70%) and chemotherapy (56%) did not exhibit a higher prevalence of shoulder pain at the time of examination.

Shoulder pain was not significantly associated with body mass index ($p = 0.636$), chemotherapy ($p = 0.47$), radiotherapy ($p = 0.571$), endocrine therapy ($p = 0.241$), or dominant hand ($p = 0.54$).

3.3. Prevalence and Characteristics of Painful vs. Non-Painful Shoulder on the Side of Breast Surgery in Breast Cancer Survivors

Approximately 30% (n = 23) of participants reported experiencing early postoperative shoulder pain on the ipsilateral side of the breast surgery (Table 1). At the time of ultrasound examination, 57.7% (n = 41) participants reported pain in the shoulder on the side of breast surgery, while 42.2% (n = 30) reported no pain in the ipsilateral shoulder (Table 3). There was no significant difference between these groups concerning the time elapsed since surgery ($p = 0.633$).

In approximately half of the participants with ipsilateral shoulder pain, supraspinatus (SSP) pathology was identified in 56% of cases, followed by acromioclavicular (AC) joint pathology in 39% of cases, and subacromial–subdeltoid (SASD) bursitis in 41% of cases; other diagnoses accounted for the remainder of cases (Table 3).

The type of surgical procedure, whether radical mastectomy or breast-conserving surgery, as well as the extent of axillary intervention (radical axillary or sentinel lymph node dissection), did not significantly influence the prevalence of shoulder pain ($p = 0.27$).

Upper extremity lymphedema was observed in 35% of patients on the operated side (Table 1), yet it was not associated with an increased prevalence of shoulder pain compared to the contralateral side ($p = 0.795$).

Table 3. Comparison of ultrasound findings in painful vs. non-painful shoulders on the side of breast surgery in breast cancer survivors.

		Painful (n = 41)		Non-Painful (n = 30)	
		n	**%**	**n**	**%**
AC joint	no pathology	25	61%	20	67%
	pathology	16	39%	10	33%
	mild arthrosis	11	27%	4	13%
	moderate/severe arthrosis	5	12%	6	20%
LHBT	no pathology	37	90%	28	94%
	pathology	4	10%	2	6%
	effusion	2	5%	1	3%
	tenosynovitis	2	5%	1	3%
Subscapularis	no pathology	33	80%	29	97%
	pathology	8	20%	1	3%
	partial tear	1	2%	0	0%
	calcific tendinopathy	4	10%	0	0%
	tendinosis	3	7%	1	3%
Supraspinatus	no pathology	14	34%	23	77%
	pathology	27	56%	7	23%
	partial tear	9	22%	1	3%
	full tear	8	20%	2	7%
	calcific tendinopathy	6	15%	3	10%
	tendinosis	4	10%	1	3%
Infraspinatus	no pathology	36	88%	26	87%
	pathology	5	12%	4	13%
	full tear	1	2%	0	0%
	calcific tendinopathy	3	7%	4	11%
	tendinosis	1	2%	0	0%
SASD bursitis	no	24	59%	26	87%
	yes	17	41%	4	13%
Shoulders with calcification	no	33	80%	23	77%
	yes	8	20%	7	23%

4. Discussion

The underlying cause of shoulder pain in more than 90% of symptomatic cases is rotator cuff pathology; however, such pathology has also been identified in 50% of asymptomatic individuals. The most frequently observed lesion involves the supraspinatus (SSP) tendon, affecting 45% of examined shoulders, followed by acromioclavicular (AC) joint arthrosis, which was observed in 35% of shoulders. The most common specific pathological finding was tendon tear, with supraspinatus tendon tears identified in 37 shoulders (25%). Among these, 19 (12.8%) were partial-thickness tears, and 18 (12.2%) were full-thickness tears. Khoschnau et al. demonstrated that in the general population, only full-thickness rotator cuff tears should be prioritized for consideration, as these have a significant potential to impair shoulder function [38]. Studies have shown that the clinical presentation of rotator cuff tears exhibits significant variability and may present with or without associated symptoms [39–41]. Additionally, given that many tears are asymptomatic, there is a recognized risk of these lesions progressing to symptomatic states over time [42]. Consequently, ultrasound imaging plays a crucial role in the early diagnosis, monitoring, and planning of appropriate treatment strategies.

Pathological changes, such as acromioclavicular joint osteoarthritis and partial rotator cuff tears, are generally considered natural, age-related phenomena [38]. This may partially

account for the observation that 50% of our patients were asymptomatic. Similar rotator cuff pathology was observed in both the operated and non-operated shoulders, suggesting an age-related etiology. As previously noted, these findings may be considered nonsignificant with respect to shoulder function [38].

Additionally, a substantial proportion of our patients (20%) exhibited bilateral pathology, consistent with findings from prior research on breast cancer patients [43–45]. Mafu et al. propose that the involvement of structures not directly affected by cancer treatment, combined with bilateral pathology, may indicate a systemic cause of the disease [46]. Hun Kim et al. suggest that bilateral pathology could also result from mechanical overload of the contralateral shoulder [28]. Similarly, rotator cuff pathology was equally present in both operated and non-operated shoulders. Which could be age related and, as previously stated, are nonsignificant findings considering shoulder function [38]. These findings underscore the importance of regular bilateral shoulder ultrasound examinations for early detection and comprehensive assessment.

In our study, we did not identify any correlation between known risk factors, such as cancer treatment, body mass index (BMI), hand dominance, or lymphedema, and the development of shoulder pain. This finding aligns with previous research by Hun Kim and Yang et al. (2010) on rotator cuff-related shoulder pain [32–34]. Study design limitations, including a small sample size and limited sample diversity, have been proposed as potential explanations for these results [32]. Furthermore, it is important to recognize that shoulder pain and associated pathologies may not result solely from cancer treatment itself but rather from its long-term consequences. These may include pectoralis muscle tightness, fibrosis, neuropathic changes, and misalignment of the shoulder girdle, which collectively contribute to altered biomechanics and pain [27].

Although ultrasound imaging has been shown to be a valuable diagnostic tool, it should be taken into account that subacromial pain syndrome is a multifactorial condition, and reliance solely on pathological findings in the rotator cuff is insufficient for a proper diagnosis. Other physical and psychological factors may significantly influence the severity and presentation of the disease, underscoring the importance of a comprehensive clinical evaluation [47].

Study Limitations

Our study has several limitations that warrant consideration:

Sample size and control group: the study sample was relatively small, and the control group could be expanded to include healthy women matched by age. This limitation restricts the generalizability of the findings and highlights the need for a larger, more representative cohort in future studies.

Cross-sectional design: as a cross-sectional study, we were unable to determine the temporal relationship between exposure and outcomes since data were collected at a single time point. This limits our ability to establish causality. Future research should adopt longitudinal designs with extended follow-ups from diagnosis to at least 2–5 years post-treatment to assess causality and long-term outcomes of painful shoulder conditions and rotator cuff pathology.

Despite efforts to maintain blinding during ultrasonography examination, the physical interaction required during ultrasonography could introduce detection bias.

Characterization of subacromial pain syndrome: in this study, subacromial pain syndrome was defined primarily by pain, without addressing other critical components such as limited range of motion, muscle weakness, functional impairments, and quality of life. Inclusion of these factors in future studies would provide a more comprehensive understanding of upper limb dysfunction.

Extrinsic factor analysis: detailed analysis of extrinsic factors such as shoulder girdle alignment, altered kinematics, and muscle performance was not included in our study. Future research should explore these aspects to better understand their impact on shoulder pathology and rehabilitation outcomes.

Addressing these limitations in future studies will enhance the robustness and clinical applicability of findings in this domain.

5. Conclusions

This study demonstrates a high prevalence of rotator cuff pathology in breast cancer survivors, regardless of the breast surgery side. The most commonly observed lesions involved the supraspinatus tendon, followed by acromioclavicular joint arthrosis, with significant pathology detected in both symptomatic and asymptomatic individuals. The similar distribution of pathology on both sides suggests that age-related changes may contribute to these findings, independent of cancer treatment.

The absence of a clear correlation between shoulder pain and known risk factors such as cancer treatment, BMI, hand dominance, or lymphedema highlights the complexity of chronic shoulder pain in breast cancer survivors. These findings emphasize that shoulder dysfunction likely arises from multifactorial causes, including long-term treatment effects, altered biomechanics, and systemic or mechanical factors.

While ultrasound remains a valuable tool for detecting structural changes, its findings must be interpreted within a comprehensive clinical context, as subacromial pain syndrome is a multifactorial condition. A multidisciplinary approach that integrates imaging, physical examination, and consideration of psychological factors is essential for accurate diagnosis and effective management of shoulder pain in breast cancer survivors.

Future research with larger and more diverse cohorts is needed to further clarify the underlying mechanisms of shoulder pain in breast cancer survivors and to optimize treatment strategies aimed at improving functional outcomes and quality of life in this population.

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References

1. Ferlay, J.; Colombet, M.; Soerjomataram, I.; Parkin, D.M.; Piñeros, M.; Znaor, A.; Bray, F. Cancer statistics for the year 2020: An overview. *Int. J. Cancer* **2021**, *149*, 778–789. [CrossRef] [PubMed]
2. World Health Organization. Breast Cancer 2021. Available online: https://www.who.int/news-room/fact-sheets/detail/breast-cancer#:=In%202020,%20there%20were%202.3,the%20world%E2%80%99s%20most%20prevalent%20cancer (accessed on 20 October 2024).
3. Berry, D.A.; Cronin, K.A.; Plevritis, S.K.; Fryback, D.G.; Clarke, L.; Zelen, M.; Mandelblatt, J.S.; Yakovlev, A.Y.; Habbema, J.D.; Feuer, E.J.; et al. Effect of screening and adjuvant therapy on mortality from breast cancer. *N. Engl. J. Med.* **2005**, *353*, 1784–1792. [CrossRef]
4. Hidding, J.T.; Beurskens, C.H.; van der Wees, P.J.; van Laarhoven, H.W.; Nijhuis-van der Sanden, M.W. Treatment related impairments in arm and shoulder in patients with breast cancer: A systematic review. *PLoS ONE* **2014**, *9*, e96748. [CrossRef] [PubMed]
5. Hayes, S.C.; Johansson, K.; Stout, N.L.; Prosnitz, R.; Armer, J.M.; Gabram, S.; Schmitz, K.H. Upper-body morbidity after breast cancer: Incidence and evidence for evaluation, prevention, and management within a prospective surveillance model of care. *Cancer* **2012**, *118* (Suppl. S8), 2237–2249. [CrossRef]
6. Schmitz, K.H.; Speck, R.M.; Rye, S.A.; DiSipio, T.; Hayes, S.C. Prevalence of breast cancer treatment sequelae over 6 years of follow-up: The Pulling Through Study. *Cancer* **2012**, *118* (Suppl. S8), 2217–2225. [CrossRef]
7. Hudson, M.; Connor, T.O. NCCN Harmonized GuidelinesTM for Sub-Saharan Africa: Survivorship. 2021. Available online: https://www.nccn.org/home/news/newsdetails?NewsID=984 (accessed on 18 October 2024).
8. Cardoso, F.; Bese, N.; Distelhorst, S.R.; Bevilacqua, J.L.; Ginsburg, O.; Grunberg, S.M.; Gralla, R.J.; Steyn, A.; Pagani, O.; Partridge, A.H.; et al. Supportive care during treatment for breast cancer: Resource allocations in low- and middle-income countries. A Breast Health Global Initiative 2013 consensus statement. *Breast* **2013**, *22*, 593–605. [CrossRef] [PubMed]
9. Distelhorst, S.R.; Cleary, J.F.; Ganz, P.A.; Bese, N.; Camacho-Rodriguez, R.; Cardoso, F.; Ddungu, H.; Gralow, J.R.; Yip, C.H.; Anderson, B.O.; et al. Optimisation of the continuum of supportive and palliative care for patients with breast cancer in low-income and middle-income countries: Executive summary of the Breast Health Global Initiative, 2014. *Lancet Oncol.* **2015**, *16*, e137–e147. [CrossRef]
10. World Health Organisation. *New Global Breast Cancer Initiative Highlights Renewed Commitment to Improve Survival*; World Health Organisation: Geneva, Switzerland, 2021; Available online: https://www.who.int/news/item/08-03-2021-new-global-breast-cancer-initiative-highlights-renewed-commitment-to-improve-survival (accessed on 21 November 2024).
11. Ong, W.L.; Schouwenburg, M.G.; van Bommel, A.C.M.; Stowell, C.; Allison, K.H.; Benn, K.E.; Browne, J.P.; Cooter, R.D.; Delaney, G.P.; Duhoux, F.P.; et al. A Standard Set of Value-Based Patient-Centered Outcomes for Breast Cancer: The International Consortium for Health Outcomes Measurement (ICHOM) Initiative. *JAMA Oncol.* **2017**, *3*, 677–685. [CrossRef]
12. Ferrell, B.R.; Grant, M.M.; Funk, B.; Otis-Green, S.; Garcia, N. Quality of life in breast cancer survivors as identified by focus groups. *Psychooncology* **1997**, *6*, 13–23. [CrossRef]
13. Bruner, D.W.; Wasserman, T. The impact on quality of life by radiation late effects. *Int. J. Radiat. Oncol. Biol. Phys.* **1995**, *31*, 1353–1355. [CrossRef]
14. Swedborg, I.; Wallgren, A. The effect of pre- and postmastectomy radiotherapy on the degree of edema, shoulder-joint mobility, and gripping force. *Cancer* **1981**, *47*, 877–881. [CrossRef] [PubMed]
15. Tobin, M.B.; Lacey, H.J.; Meyer, L.; Mortimer, P.S. The psychological morbidity of breast cancer-related arm swelling. Psychological morbidity of lymphoedema. *Cancer* **1993**, *72*, 3248–3252. [CrossRef]
16. Johansen, J.; Overgaard, J.; Blichert-Toft, M.; Overgaard, M. Treatment of morbidity associated with the management of the axilla in breast-conserving therapy. *Acta Oncol.* **2000**, *39*, 349–354. [CrossRef]
17. Lee, T.S.; Kilbreath, S.L.; Refshauge, K.M.; Herbert, R.D.; Beith, J.M. Prognosis of the upper limb following surgery and radiation for breast cancer. *Breast Cancer Res. Treat.* **2008**, *110*, 19–37. [CrossRef] [PubMed]
18. Rietman, J.S.; Dijkstra, P.U.; Hoekstra, H.J.; Eisma, W.H.; Szabo, B.G.; Groothoff, J.W.; Geertzen, J.H. Late morbidity after treatment of breast cancer in relation to daily activities and quality of life: A systematic review. *Eur. J. Surg. Oncol.* **2003**, *29*, 229–238. [CrossRef] [PubMed]
19. Vignes, S.; Arrault, M.; Dupuy, A. Factors associated with increased breast cancer-related lymphedema volume. *Acta Oncol.* **2007**, *46*, 1138–1142. [CrossRef]
20. Armer, J.M.; Stewart, B.R. A comparison of four diagnostic criteria for lymphedema in a post-breast cancer population. *Lymphat. Res. Biol.* **2005**, *3*, 208–217. [CrossRef]
21. Rönkä, R.H.; Pamilo, M.S.; von Smitten, K.A.; Leidenius, M.H. Breast lymphedema after breast conserving treatment. *Acta Oncol.* **2004**, *43*, 551–557. [CrossRef]
22. Nesvold, I.L.; Fosså, S.D.; Holm, I.; Naume, B.; Dahl, A.A. Arm/shoulder problems in breast cancer survivors are associated with reduced health and poorer physical quality of life. *Acta Oncol.* **2010**, *49*, 347–353. [CrossRef] [PubMed]

23. Levangie, P.K.; Drouin, J. Magnitude of late effects of breast cancer treatments on shoulder function: A systematic review. *Breast Cancer Res. Treat.* **2009**, *116*, 1–15. [CrossRef]
24. Tsai, R.J.; Dennis, L.K.; Lynch, C.F.; Snetselaar, L.G.; Zamba, G.K.; Scott-Conner, C. The risk of developing arm lymphedema among breast cancer survivors: A meta-analysis of treatment factors. *Ann. Surg. Oncol.* **2009**, *16*, 1959–1972. [CrossRef]
25. Meeske, K.A.; Sullivan-Halley, J.; Smith, A.W.; McTiernan, A.; Baumgartner, K.B.; Harlan, L.C.; Bernstein, L. Risk factors for arm lymphedema following breast cancer diagnosis in Black women and White women. *Breast Cancer Res. Treat.* **2009**, *113*, 383–391. [CrossRef]
26. Hayes, S.C.; Rye, S.; Battistutta, D.; DiSipio, T.; Newman, B. Upper-body morbidity following breast cancer treatment is common, may persist longer-term and adversely influences quality of life. *Health Qual Life Outcomes.* **2010**, *8*, 92. [CrossRef]
27. Ebaugh, D.; Spinelli, B.; Schmitz, K.H. Shoulder impairments and their association with symptomatic rotator cuff disease in breast cancer survivors. *Med. Hypotheses* **2011**, *77*, 481–487. [CrossRef]
28. Stubblefield, M.D.; Keole, N. Upper body pain and functional disorders in patients with breast cancer. *PM R* **2014**, *6*, 170–183. [CrossRef]
29. Herrera, J.E.; Stubblefield, M.D. Rotator cuff tendonitis in lymphedema: A retrospective case series. *Arch. Phys. Med. Rehabil.* **2004**, *85*, 1939–1942. [CrossRef]
30. Jeong, H.J.; Sim, Y.J.; Hwang, K.H.; Kim, G.C. Causes of shoulder pain in women with breast cancer-related lymphedema: A pilot study. *Yonsei Med. J.* **2011**, *52*, 661–667. [CrossRef]
31. Strakowski, J.A.; Visco, C.J. Diagnostic and therapeutic musculoskeletal ultrasound applications of the shoulder. *Muscle Nerve* **2019**, *60*, 1–6. [CrossRef] [PubMed]
32. Kim, J.H.; Kim, S.H.; Kim, H.R.; Lee, S.H.; Yoon, S.Y.; Yang, J.H.; Yoo, Y.B.; Park, K.S.; Nam, S.E.; Hong, S.; et al. Ultrasonographic evaluation of chronic shoulder pain after breast cancer surgery: Single center, cross-sectional study. *Sci. Rep.* **2020**, *10*, 16792. [CrossRef] [PubMed]
33. Gala-Alarcón, P.; Prieto-Gómez, V.; Bailón-Cerezo, J.; Yuste-Sánchez, M.J.; Arranz-Martín, B.; Torres-Lacomba, M. Changes in shoulder outcomes using ultrasonographic assessment of breast cancer survivors: A prospective longitudinal study with 6-month follow-up. *Sci. Rep.* **2021**, *11*, 23016. [CrossRef] [PubMed]
34. Yang, E.J.; Park, W.B.; Seo, K.S.; Kim, S.W.; Heo, C.Y.; Lim, J.Y. Longitudinal change of treatment-related upper limb dysfunction and its impact on late dysfunction in breast cancer survivors: A prospective cohort study. *J. Surg. Oncol.* **2010**, *101*, 84–91. [CrossRef]
35. Duan, L.; Zhao, L.; Liu, Y.; Zhang, Y.; Zheng, W.; Yu, X.; Liu, H.; Li, Z.; Peng, Z.; Li, X. Neuralgic amyotrophy: Sensitivity and specificity of magnetic resonance neurography in diagnosis: A retrospective study. *Medicine* **2023**, *102*, e35527. [CrossRef]
36. Czerniec, S.A.; Ward, L.C.; Refshauge, K.M.; Beith, J.; Lee, M.J.; York, S.; Kilbreath, S.L. Assessment of breast cancer-related arm lymphedema--comparison of physical measurement methods and self-report. *Cancer Investig.* **2010**, *28*, 54–62. [CrossRef]
37. Selame, L.A.J.; Matsas, B.; Krauss, B.; Goldsmith, A.J.; Shokoohi, H. A Stepwise Guide to Performing Shoulder Ultrasound: The Acromio-Clavicular Joint, Biceps, Subscapularis, Impingement, Supraspinatus Protocol. *Cureus* **2021**, *13*, e18354. [CrossRef] [PubMed]
38. Khoschnau, S.; Milosavjevic, J.; Sahlstedt, B.; Rylance, R.; Rahme, H.; Kadum, B. High prevalence of rotator cuff tears in a population who never sought for shoulder problems: A clinical, ultrasonographic and radiographic screening study. *Eur. J. Orthop. Surg. Traumatol.* **2020**, *30*, 457–463. [CrossRef] [PubMed]
39. Moosmayer, S.; Smith, H.J.; Tariq, R.; Larmo, A. Prevalence and characteristics of asymptomatic tears of the rotator cuff: An ultrasonographic and clinical study. *J. Bone Jt. Surg. Br.* **2009**, *91*, 196–200. [CrossRef] [PubMed]
40. Yamaguchi, K.; Ditsios, K.; Middleton, W.D.; Hildebolt, C.F.; Galatz, L.M.; Teefey, S.A. The demographic and morphological fetures of rotator cuff disease. A comparison of asymptomatic and symptomatic shoulders. *J. Bone Jt. Surg. Am.* **2006**, *88*, 1699–1704. [CrossRef] [PubMed]
41. Mall, N.A.; Kim, H.M.; Keener, J.D.; Steger-May, K.; Teefey, S.A.; Middleton, W.D.; Stobbs, G.; Yamaguchi, K. Symptomatic progression of asymptomatic rotator cuff tears: A prospective study of clinical and sonographic variables. *J. Bone Joint Surg. Am.* **2010**, *92*, 2623–2633. [CrossRef] [PubMed]
42. Yamaguchi, K.; Tetro, A.M.; Blam, O.; Evanoff, B.A.; Teefey, S.A.; Middleton, W.D. Natural history of asymptomatic rotator cuff tears: A longitudinal analysis of asymptomatic tears detected sonographically. *J. Shoulder Elbow Surg.* **2001**, *10*, 199–203. [CrossRef]
43. Shamley, D.; Lascurain-Aguirrebeña, I.; Oskrochi, R.; Srinaganathan, R. Shoulder morbidity after treatment for breast cancer is bilateral and greater after mastectomy. *Acta Oncol.* **2012**, *51*, 1045–1053. [CrossRef]
44. Sagen, A.; Kaaresen, R.; Sandvik, L.; Thune, I.; Risberg, M.A. Upper limb physical function and adverse effects after breast cancer surgery: A prospective 2.5-year follow-up study and preoperative measures. *Arch. Phys. Med. Rehabil.* **2014**, *95*, 875–881. [CrossRef]

45. Adriaenssens, N.; Vinh-Hung, V.; Miedema, G.; Versmessen, H.; Lamote, J.; Vanhoeij, M.; Lievens, P.; van Parijs, H.; Storme, G.; Voordeckers, M.; et al. Early contralateral shoulder-arm morbidity in breast cancer patients enrolled in a randomized trial of post-surgery radiation therapy. *Breast Cancer* **2012**, *6*, 79–93. [CrossRef]
46. Mafu, T.S.; September, A.V.; Shamley, D. The potential role of angiogenesis in the development of shoulder pain, shoulder dysfunction, and lymphedema after breast cancer treatment. *Cancer Manag. Res.* **2018**, *10*, 81–90. [CrossRef]
47. Hinsley, H.; Ganderton, C.; Arden, N.K.; Carr, A.J. Prevalence of rotator cuff tendon tears and symptoms in a Chingford general population cohort, and the resultant impact on UK health services: A cross-sectional observational study. *BMJ Open* **2022**, *12*, e059175. [CrossRef] [PubMed]

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High-Frequency Ultrasonography Imaging: Anatomical Measuring Site as Potential Clinical Marker for Early Identification of Breast Cancer-Related Lymphedema

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Abstract: Background/Objectives: Accurate diagnosis of breast cancer-related lymphedema remains a clinical challenge. This study evaluated the diagnostic utility of ultrasound in detecting early lymphedema compared to conventional criteria, including the International Society of Lymphology staging and limb volume measurements. **Methods**: In this retrospective cross-sectional study, 68 female participants with unilateral breast cancer, who had completed cancer treatment at least six months before study enrolment, underwent both ultrasonographic assessment and standard limb circumference measurements. Ultrasound was performed bilaterally at five standardized anatomical sites. Sonographic parameters included assessment of cutaneous and subcutaneous thickness and echogenicity. Clinical staging and symptom profiles were assessed using ISL criteria and a structured questionnaire. Volume status was determined by relative volume change (RVC). **Results**: Among 68 participants, 36 were classified as ISL stage 0 and 32 as ISL stage II, 30 had RVC < 5%, while 38 had RVC $\geq$ 5%. Advanced stages were associated with older age. Multivariate analysis identified increased skin thickness at the medial upper arm cutis as significantly correlated with RVC $\geq$ 5% (OR 1.49, 95% CI: 1.01–2.21, $p = 0.047$). A similar trend was observed at the medial forearm (OR 1.3 (95% CI: (0.99, 1.71))). **Conclusions**: This study highlights ultrasound's potential for early breast cancer-related lymphedema detection, especially in patients with minimal volume changes where conventional methods fall short. Increased cutaneous thickness in the medial upper arm emerged as a sensitive marker of early disease, while subcutaneous thickness and echogenicity may reflect in advanced stages. This distinction underscores the clinical value of cutaneous thickness as a potential clinical key marker for early lymphedema detection, emphasizing the need for standardized protocols and defined thresholds to guide timely interventions.

Keywords: lymphedema; breast cancer; diagnostic ultrasound; cross-sectional anatomy; disease early detection

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1. Introduction

Breast cancer-related lymphedema (BCRL) commonly arises from lymphatic system impairment following lymph node dissection, other surgical intervention, or radiation

therapy, resulting in disrupted lymphatic flow [1]. This impairment leads to the accumulation of lymphatic fluid, causing structural alterations in the skin and subcutaneous compartments [2]. Clinically, BCRL may manifest as progressive swelling of the arm, shoulder, neck, or torso, often accompanied by discomfort, tightness, and heaviness, ultimately contributing to functional impairment and diminished quality of life [1,3,4].

The true incidence of BCRL is challenging to ascertain due to variability in diagnostic methodologies, treatment modalities, and patient-specific factors [5–7]. The reported incidence of arm BCRL is approximately 21% [6,7]. Although current surveillance models emphasize early detection, BCRL often remains undiagnosed until pronounced swelling occurs [8,9]. Delayed diagnosis hampers early intervention, reducing treatment efficacy and adversely impacting patient functionality and quality of life [10–14].

Preventing BCRL progression is critical and necessitates timely intervention upon recognition of early signs [15–18]. Prevention strategies include primary prevention, aiming to avoid disease onset; secondary prevention, focusing on early-stage treatment to inhibit disease progression; and tertiary prevention, managing advanced-stage BCRL [19,20]. Despite the existence of prevention guidelines, they often rely on anecdotal recommendations lacking robust empirical support, leaving clinicians without proper prevention strategies [10]. The gold standard rehabilitation strategy of BCRL is complete decongestive therapy (CDT), which should be individually tailored depending on disease severity and includes compression therapy, manual lymphatic drainage, exercise, skin care, and patient education [11–13,15,17–20].

Accurate early diagnosis of BCRL remains challenging due to reliance on subjective clinical assessment, volumetric measurements, and patient-reported symptoms, which often lack precision and specificity [6,10,21]. The International Society of Lymphology (ISL) classifies subclinical BCRL primarily by patient's perception of swelling [10,22]. Subjective assessments, such as palpation and patient-reported symptoms, often demonstrate inconsistencies, reducing diagnostic reliability [23,24]. Although circumferential and volumetric measurements are reliable for assessing total limb volume, including bones, muscles, fat, and other soft tissues, they lack specificity for BCRL [17,24–26]. Volume increases may reflect fluid accumulation or pathological tissue proliferation, which standard methods cannot distinguish, risking misinterpretation of underlying skin changes [10,13,23,27,28].

Advanced imaging modalities such as computed tomography, magnetic resonance imaging, lymphoscintigraphy, and indocyanine green lymphography provide more detailed visualization of lymphatic structures. Still, they are limited by high costs, invasiveness, and poor portability [19,24,29].

Effective BCRL management necessitates a simple, accessible diagnostic tool to confirm subjective findings at the earliest stage, enabling differentiation between subclinical and clinical BCRL. Emerging research suggests that high-resolution ultrasonography (US) may be a valuable tool for precise BCRL assessment and accurate management. However, it is not yet widely implemented in clinical practice [29–39].

Other non-invasive modalities, including bioimpedance spectroscopy (BIS) and tissue dielectric constant (TDC) measurements, provide advantages in cost, portability, and effective use but lack the anatomical resolution provided by US. While US requires more training and operator expertise, it provides superior visualization of subcutaneous tissues and is particularly valuable in ambiguous cases [40,41].

Previous US studies have primarily focused on advanced-stage BCRL, highlighting the correlation between subcutaneous echogenicity and disease severity [31,37]. Ultrasound effectively distinguishes various progression patterns by identifying variations in echogenicity and echo-free spaces, therefore providing valuable insights into edema and fi-

brosis in the skin and subcutaneous tissues and serving as a reliable method for monitoring treatment outcomes or disease progression over time [37,42,43].

Despite promising applications, standardized ultrasonographic protocol for assessing subclinical-stage BCRL remains underdeveloped, emphasizing the need for further research and clinical validation [3,31,33–39,44–47].

Current scarce literature reveals considerable methodological variability across studies of upper limb BCRL, including cross-sectional, diagnostic accuracy, longitudinal, prospective, and retrospective designs [2–4,31,35,45,47–49]. Variations also arise in participant selection, lymphedema definitions, staging, and post-breast cancer surgery duration [3,39,46]. Ultrasound modalities applied in research include elastography, high-frequency grayscale, and B-mode ultrasound, typically ranging from 11 to 18 MHz [2–4,31,35,45,47–49]. Measurement protocols differ in assessed parameters such as tissue thickness, echogenicity, cross-sectional area changes, and anatomical reference points, resulting in limited comparability [3,45,47]. Additionally, inconsistencies between absolute thickness measurements and relative indicators complicate standardization efforts [3,32,43,50,51]. Establishing uniform ultrasound protocols with clearly defined anatomical landmarks is critical to enhance clinical validity and comparability across studies [2,3].

This study aims to assess the effectiveness of US in early detection and management of lymphedema (LE) in breast cancer survivors by comparing its diagnostic reliability with conventional methods such as the ISL staging system and limb volume measurements. Specifically, our research seeks to determine whether US can identify subclinical LE changes before they become apparent through traditional assessments, facilitating earlier intervention and potentially improving patient outcomes. Additionally, the study evaluates the consistency and accuracy of US measurements relative to established diagnostic tools, aiming to develop standardized protocols for US integration into routine clinical practice.

2. Materials and Methods

2.1. Ethical Approval

The study protocol was approved by the Ethical Committee of the University Hospital Split (protocol code 2181-147/01/06/LJ.Z.-23-2). This study was conducted following the principles of the Declaration of Helsinki. Before enrolment in the study, all participating women were informed about the nature of the study, and written informed consent was obtained.

2.2. Study Population

Seventy-nine breast cancer survivors participated in this cross-sectional observational study from 1 November 2023 to 30 April 2024. All breast cancer survivors, referred to the University Hospital Split Lymphedema Clinic during the study period, were consecutively screened for eligibility and invited to participate in the study. The eligibility criteria of the study population were women aged 18 years or older who had completed treatment for unilateral breast cancer at least six months before study enrolment. The exclusion criteria were women with bilateral or metastatic breast cancer, cognitive impairments, pre-existing arm lymphedema before the initiation of breast cancer treatment, and active lymphedema treatment within three months before enrolment. Following these exclusion criteria, data from 11 participants were excluded from the final analysis. Therefore, the final analysis was conducted on 68 breast cancer survivors (Figure 1).

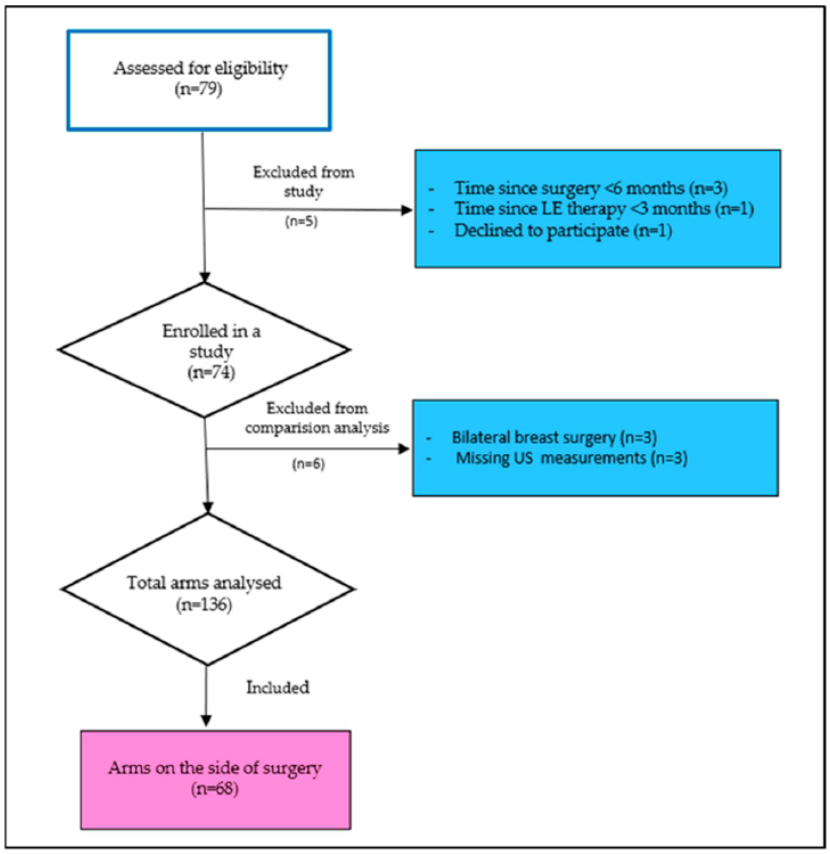

Figure 1. Flowchart of participants' enrolment.

2.3. Measurements and Data Collection

All participants underwent a single evaluation session at the University Hospital Split as part of this cross-sectional study. A trained researcher obtained baseline demographic data and a detailed medical history through structured clinical interviews and self-administered questionnaires. Missing data were addressed by reviewing participants' electronic medical records. Table 1 summarizes the demographic and disease-related characteristics of the participants.

Table 1. Demographics and disease-related characteristics of study participants.

Variable	Lymphedema Stage		*p*-Value	Lymphedema RVC [6]		*p*-Value
	ISL [5] 0 (*n* = 36)	ISL [5] 2 (*n* = 32)		RVC [6] < 5% (*n* = 30)	RVC [6] ≥ 5% (*n* = 38)	
Age, mean (SD)	54.64 ± 8.15	61.63 ± 7.13	<0.001	54.77 ± 7.8	60.7 ± 8.2	0.003
BMI [1], median (IQR)	26.35 (8.03)	27.1 (4.5)	0.551	26.9 (7.3)	27.1 (5.5)	0.780
Dominant is affected limb, n (%)	22 (61.1%)	20 (62.5%)	0.906	17 (56.7%)	25 (65.8%)	0.442
Time since BC [2] surgery, median (IQR)	4.5 (6.0)	5.0 (9.0)	0.558	4.0 (5.0)	5.0 (7.8)	0.857
Type of surgery, n (%)			0.167			0.081

Table 1. *Cont.*

Variable	Lymphedema Stage		*p*-Value	Lymphedema RVC [6]		*p*-Value
	ISL [5] 0 (*n* = 36)	ISL [5] 2 (*n* = 32)		RVC [6] < 5% (*n* = 30)	RVC [6] ≥ 5% (*n* = 38)	
Mastectomy	25 (69.4%)	17 (53.1%)		22 (73.3%)	20 (52.6%)	
Breast-conserving surgery	11 (30.6%)	15 (46.9%)		8 (26.7%)	18 (47.4%)	
Type of lymph node removal, n (%)			0.058			0.988
SLND [3]	17 (47.2%)	8 (25.0%)		11 (36.7%)	14 (36.8%)	
ALND [4]	19 (52.7%)	24 (75.0%)		19 (63.3%)	26 (68.4%)	
Post-surgery complications, n (%)	26 (72.2%)	22 (68.8%)	0.754	20 (66.7%)	28 (73.7%)	0.528
Axillary web syndrome n (%)	9 (25%)	6 (18.8%)	0.535	8 (26.7%)	7 (18.4%)	0.416
Radiotherapy application, n (%)	23 (63.9%)	26 (81.3%)	0.111	21 (70%)	28 (73.7%)	0.737
Chemotherapy application, n (%)	19 (52.8%)	19 (59.4%)	0.584	14 (46.7%)	24 (63.2%)	0.174
Type of chemotherapy application, n (%)		0.935			0.950	
Adjuvant	16 (44.4%)	15 (46.9%)		12 (40%)	19 (50.0%)	
Neoadjuvant	4 (11.1%)	4 (12.5%)		1 (3.3%)	3 (7.9%)	
Anti HER2 application, n (%)	7 (19.4%)	5 (15.6%)	0.771	6 (20.0%)	6 (15.8%)	0.383
Endocrine treatment, n (%)	27 (8%)	23 (71.9%)	0.771	25 (83.3%)	25 (65.8%)	0.103

[1] Body mass index, [2] breast cancer, [3] sentinel lymph node dissection, [4] axillary lymph node dissection, [5] International Society of Lymphology classification, [6] relative volume change.

2.4. Lymphedema Assessment and Classification

2.4.1. International Society of Lymphology (ISL) Classification

A physical medicine and rehabilitation specialist (A.P.) with expertise in lymphedema diagnosis and treatment conducted clinical staging of lymphedema according to ISL lymphedema severity staging criteria [10]. Subclinical lymphedema classified as Stage 0—included participants at risk of developing breast cancer lymphedema with lymph system obstruction due to the breast cancer treatment, with swelling not yet detectable but subtle tissue changes and self-reported symptoms possibly present. Clinical LE was classified as Stage I–III. In Stage I, reversible early fluid accumulation can be resolved with limb elevation. Stage II includes irreversible change, structural tissue changes, and moderate swelling, with early pitting or late-stage non-pitting edema due to fat and fibrotic changes. Stage III is characterized by severe swelling, trophic skin changes (e.g., acanthosis, fibrosis, fat deposits), and development of skin overgrowths [10,37].

2.4.2. Limb Circumference Measurement

Limb circumference measurements were independently performed by two experienced and trained physiotherapists. To ensure consistency, two physiotherapists (I.K.K. and J.G.) jointly practiced the standardized measurement protocol before data collection to align their techniques and reduce potential variability in measurement methods. To evaluate inter- and intra-observer reliability, 20% of participants were randomly selected for repeated measurements by blinded physiotherapists concerning prior results to ensure objectivity. To ensure intra-rater reliability, one physiotherapist re-measured the same participants at a separate time point under the same conditions, again blinded to prior results. Additionally, inter-rater reliability was conducted by two physiotherapists who measured the same participants independently and separately, without previous knowledge of each other's results. Intraclass Correlation Coefficients for both intra- and inter-rater reliability were excellent (ICC $\geq$ 0.99) except for the third measuring point with moderate inter-rater

reliability (ICC $\geq$ 0.65). To perform adequate measurements, participants were seated with their arm resting on an adjustable hydraulic table with their shoulders flexed at approximately 90° and their forearm in pronation [23]. Five measurements were taken every 10 cm at predetermined points along the arm starting at the ulnar styloid process of the wrist (designated as point 0) using a flexible Juzo tape with 1 mm accuracy. Measurements were repeated three times at each point. Average values were documented on a standardized form [23,44]. In this study, we used the most commonly applied objective clinical diagnostic cut-off criteria, interlimb circumference measurement difference $\geq$ 2 cm taken at any single measuring site along the upper extremity [27,52].

2.4.3. Derived Limb Volume Measurements

The absolute limb volumes of affected and unaffected arms were computed using the truncated cone formula across four segmental volumes (0–10 cm, 10–20 cm, 20–30 cm, and 30–40 cm), as described in the literature [53,54]. Limb volume ratio was derived as the relative volume change (RVC) between the affected and unaffected arms, normalized to the contralateral arm volume [26,55,56]. Clinical diagnosis was set at RVC 10%, which helped rule in BCRL, but values below RVC 10% could be used to rule out [26,52]. Since this study aimed to identify early BCRL, it was recommended to adjust diagnostic criteria to a low diagnostic volume threshold of RVC $\geq$ 5% [17,20,23,26,39,57]. In this study, we did a subgroup analysis to detect BCRL set at RVC $\geq$ 10% and RVC $\geq$ 5% volume diagnostic thresholds.

2.4.4. Patient Self-Perceived Lymphedema

As in previous research, self-perceived lymphedema was considered if the participant answered positively to a question asked by the researcher, "At the moment, does your arm at the side of the surgery feel swollen?" [58–60].

Women who reported self-perceived lymphedema were further investigated about the presence of specific symptoms in their arm, such as tightness, burning, numbness, feeling of pins and needles, feeling of heaviness, feeling of tight clothes, feeling of tight jewellery, and pain sensation [58–60].

2.4.5. Ultrasound Examination of Upper Limbs

Each participant underwent an ultrasound examination of the breast, axillary lymph nodes, and upper limbs during the evaluation session. Ultrasound measurements were performed using a high-frequency linear probe (9–12 MHz) on an ultrasound system, SuperSonic Imagine Aixplorer MACH 30, Aix-en-Provence, France. The affected upper limb was evaluated to assess the skin's and subcutaneous tissue's thickness and sonographic characteristics. For comparison, the contralateral, non-affected limb was also examined.

In the initial measurement position, participants were seated with their upper arm slightly abducted, elbow fully extended, and hand in supination. For the fifth measurement, participants placed their hands in a pronated position on the dorsal side of the hand. Measurement points were marked at five locations on each limb using a non-stretched centimetre tape, as described in the literature [15]: Upper arm medial and upper arm lateral, 7 cm above the cubital crease; medial and lateral forearm, 7 cm below the cubital crease; and dorsal hand surface, mid-point between the wrist and the first metacarpophalangeal joint. A total of 10 measurement sites per participant were assessed, 5 on each arm (Figure 2).

After applying a gel layer between the transducer and the skin, the transducer was placed at each site perpendicular to the skin with minimal pressure to avoid compressing the measured tissue layers. At each site, the thickness of the skin and subcutaneous tissue was recorded in centimetres and compared with the corresponding site on the contralateral arm. Subcutaneous tissue thickness was defined as the distance from the

posterior echogenic border of the dermis to the anterior echogenic border of the deep muscular fascia. Additionally, the sonographic pattern of the subcutaneous tissue was assessed and classified as "normal", "sclerotic", "fluid", or "no clear border between skin and subcutaneous tissue" according to Mander et al.'s proposed classification system [3].

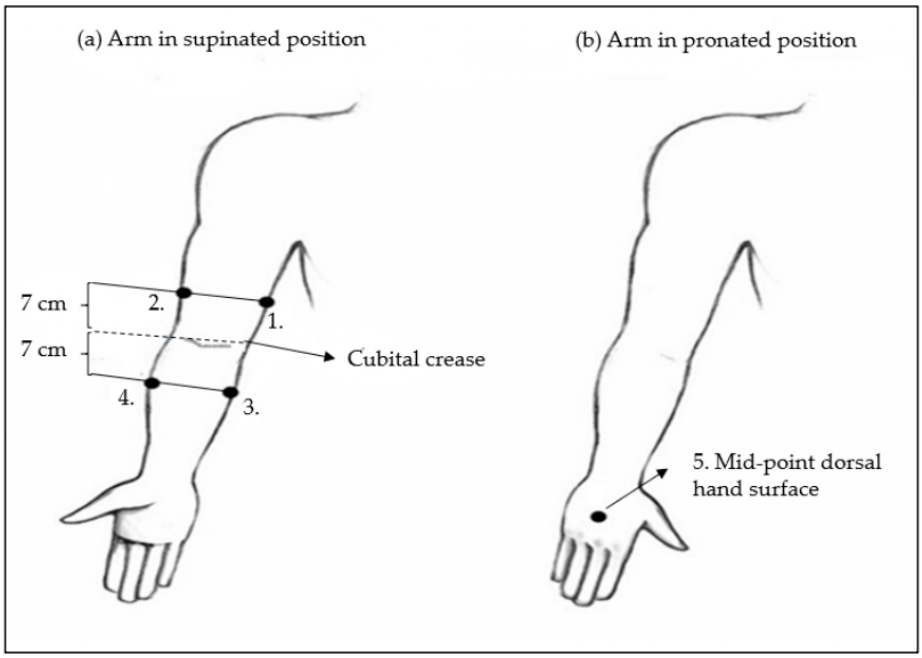

Figure 2. Schematic representation of ultrasound arm measuring points for cutis and subcutis thickness determination. (**a**) Arm positioned in supinated position: 1. Medial upper arm and 2. Lateral upper arm measuring points are placed 7 cm above the cubital crease. 3. Medial forearm and 4. Lateral forearm measuring points are placed 7 cm below the cubital crease. (**b**) Arm in pronated position: 5. Mid-point dorsal hand surface measuring point is placed between the wrist and the first metacarpophalangeal joint.

All measurements were performed in the early morning to control for diurnal variation in skin water content. They were conducted by an experienced radiologist with over 10 years of expertise in ultrasound imaging who completed additional training specific to the study protocol.

For quality assurance, two radiologists (D.B.M. and M.G.M.) practiced a standardized measurement protocol before data collection. To formally assess measurement reliability, 10% of participants were randomly reassessed by radiologists blinded to the prior results. First, radiologists measured the same participants independently and separately for inter-rater reliability. Furthermore, to ensure intra-rater reliability, one radiologist remeasured the same participants at a separate time point under the same conditions. Most measurements indicated excellent or good agreement across nearly all measurement sites, specifically, upper arm lateral skin (ICC $\geq$ 86), upper lateral subcutis (ICC $\geq$ 0.91), upper arm medial cutis (ICC $\geq$ 0.91), upper arm medial subcutis (0.89), forearm lateral cutis (ICC $\geq$ 0.94), forearm lateral subcutis (ICC $\geq$ 0.81), forearm medial cutis (ICC $\geq$ 0.95), forearm medial subcutis (ICC $\geq$ 0.98), hand cutis (ICC $\geq$ 0.96), except inter-rater reliability for the fifth measuring point, which was slightly below good agreement (ICC $\geq$ 0.73)(Appendix A).

2.5. Sample Size

The sample size was estimated based on expected changes in skin and subcutaneous thickness [48]. At least 58 participants were required to detect the between-group difference, ensuring 80% power at a 5% significance level.

2.6. Statistical Analysis

The distribution of continuous variables was assessed using the one-sample Kolmogorov–Smirnov test. Variables with a normal distribution were reported as mean ± standard deviation (SD), while non-normally distributed variables were presented as median and interquartile range (IQR). Categorical variables were summarized as frequencies and percentages. As appropriate, differences between groups were evaluated using the chi-square test for categorical variables and either Student's *t*-test or the Mann–Whitney U test for continuous variables.

We performed univariate analyses to investigate associations with the dependent variables (ISL stage, cm categories, and PEV categories). Variables that reached statistical significance ($p < 0.05$) were then included in multivariable models. Given the limited number of outcome events and the potential risk of overfitting, we applied least absolute shrinkage and selection operator (LASSO) regression with 10-fold cross-validation to select relevant predictors. All candidate variables were retained by LASSO (i.e., coefficients > 0), suggesting potential importance.

Subsequently, we fitted age-adjusted multivariable logistic regression models including the LASSO-selected predictors. Odds ratios (ORs) and 95% confidence intervals (CIs) were reported. To internally validate the models and assess coefficient stability, we applied nonparametric bootstrapping with 1000 resamples. Model discrimination was evaluated using the area under the receiver operating characteristic (ROC) curve (AUC), and model calibration was assessed using the Hosmer–Lemeshow goodness-of-fit test. All statistical analyses were performed using JASP (Version 0.18.3) and R. A *p*-value < 0.05 was considered statistically significant.

3. Results

3.1. Participants' Demographics and Disease-Related Characteristics

This study analyzed a total of 68 breast cancer survivor participants' data. The period elapsed since breast cancer surgery until study enrolment was on average five years. According to BCRL ISL classification, participants were distributed into two groups: ISL Stage 0 group (ISL 0) with 36 (52.9%) and ISL Stage II group (ISL II) with 32 (47.1%) participants. Furthermore, we divided participants into two groups according to RVC category < 5% or ≥5%. Study participants in these two groups were statistically similar, except for age ($p < 0.001$), where ISL II (61.63 ± 7.13) and RVC ≥ 5% (54.64 ± 8.15) participants tended to be older.

3.2. Participants' Lymphedema Characteristics

The outcomes of LE characteristics, categorized according to the ISL stage classification, are summarized in Table 2. We analyzed the data from breast cancer participants according to their clinical stage of BCRL (ISL 0 and ISL II). We found a significant statistical difference between the groups for most BCRL characteristics ($p < 0.001$), except for pain in the affected arm ($p = 0.666$). Additionally, the outcomes of BCRL characteristics, based on volume change, are summarized in Table 3. When using the minimal detectable volume change to identify low volume LE, with a cut-off value of RVC ≥ 5%, we observed a significant statistical difference between the groups for most LE characteristics ($p < 0.001$), except for self-reported symptoms, erysipelas infections, and pain in the affected limb.

Table 2. Participants' LE characteristics according to ISL stage classification.

Variable	ISL [1] 0 (*n* = 36)	ISL [1] II (*n* = 32)	*p*-Value
Increase of interlimb edema volume ratio, n (%)			
0–5%	27 (75%)	3 (9.4%)	<0.001
>5%	9 (25%)	29 (90.6%)	
Increase of interlimb edema volume ratio, n (%)			
0–10%	35 (97.2%)	14 (43.8%)	<0.001
>10%	1	18	
Interlimb circumference difference, n (%)			
<2cm	33 (91.6%)	6 (18.8%)	<0.001
≥2 cm	3 (8.3%)	26 (81.3%)	
Self-reported swelling, n (%)	13 (36.1%)	25 (78.1%)	<0.001
Self-reported LE symptoms, n (%)	20 (55.6%)	28 (87.5%)	0.004
Lymphedema complications, n (%):			
Pain in the LE [2] affected arm	15 (41.7%)	15 (46.9%)	0.666
Erysipelas episodes	1 (2.8%)	7 (21.9%)	0.015

[1] International Society of Lymphology classification, [2] lymphedema.

Table 3. Participants' LE characteristics according to volume ≥ 5%.

Variable	RVC[2] < 5% (*n* = 30)	RVC[2] ≥ 5% (*n* = 38)	*p*-Value
ISL stage			
[1] ISL 0	27 (90%)	9 (23.7%)	<0.001
ISL II	3 (10%)	29 (76.3%)	
Interlimb circumference difference, n (%)			
<2 cm	28 (93.3%)	11 (29%)	<0.001
≥2 cm	2 (6.7%)	27 (71.1%)	
Self-reported swelling, n (%)	12 (40%)	26 (68.4%)	0.019
[2] RVC			
<10%	30 (100%)	19 (50%)	<0.001
≥10%	0 (0%)	19 (50%)	
Self-reported [3] LE symptoms, n (%)	18 (60%)	30 (78.9%)	0.055
Lymphedema complications, n (%)			
Pain in LE LE-affected arm	13 (43.3%)	17 (44.7%)	0.908
Erysipelas episodes	1 (3.3%)	7 (18.4%)	0.055

[1] International Society of Lymphology classification, [2] relative volume change, [3] lymphedema.

3.3. Factors Associated with Lymphedema Classified According to the International Society of Lymphology Classification

In the univariate analysis, significantly higher measurements were found at several points, specifically in the UaMC ($p = 0.011$) and UaMSc ($p = 0.002$) regions, as well as in the FaMC ($p = 0.001$) and FaMSc ($p = 0.001$) regions, in participants with ISL stage II LE. Additionally, increased echogenicity values were observed more frequently in individuals with ISL stage II LE ($p = 0.001$).

A multivariable logistic regression analysis was performed with the ISL stage as the dependent variable and UaMC, UaMSc, FaMC, FaMSc, and arm echogenicity as independent variables. The logistic regression model was statistically significant ($p < 0.001$, Nagelkerke $R^2 = 0.562$, accuracy = 0.765). The multivariate analysis revealed statistical significance for two variables: the FaMC area (OR 1.71, 95% CI: 1.02–2.86, $p = 0.041$) and UaMSc (OR 1.05, 95% CI: 1.002–1.1, $p = 0.041$). Specifically, as the interlimb skin thickness increased in the FaMC and UaMSc regions, the likelihood of a higher ISL stage also increased (Table 4, Supplementary Materials: Figure S1)).

Table 4. Multivariate logistic regression analysis for the prediction of ISL stage.

	ISL Classification [11]		**Univariate Model**	**Multivariable Model**	
Variable	ISL = 0 [12]	ISL = II [13]	*p*-Value	OR [14] (95% C.I)	*p*-Value
UaLC [1], median (IQR)	2.0 (2.5)	3.0 (4.0)	0.061		
UaLSc [2], median (IQR)	11.5 (16.25)	10.5 (19.25)	0.535		
UaMC [3], median (IQR)	1.5 (1.5)	3.0 (5.0)	0.011	1.32 (0.90, 1.95)	0.158
UaMSc [4], median (IQR)	14.0 (14.25)	27.0 (32.25)	0.002	1.05 (1.002, 1.1)	0.041
FaLC [5], median (IQR)	2.0 (1.0)	1.5 (3.0)	0.342		
FaLSc [6], median (IQR)	6.0 (7.25)	6.5 (9.5)	0.805		
FaMC [7], median (IQR)	1.0 (1.0)	2.5(6.25)	0.001	1.71 (1.02, 2.86)	0.041
FaMSc [8], median (IQR)	5.5 (7.5)	10.0 (22.25)	0.001	0.98 (0.93, 1.03)	0.431
HC [9], median (IQR)	12.5 (7.0)	12.5 (9.0)	0.961		
HSc [10], median (IQR)	2.0 (2.25)	2.0 (3.5)	0.737		
Arm echogenity n (%)					
Increased echogenicity	5 (22.7%)	17 (77.3%)	<0.001	reference	0.272
Normal echogenity	31 (67.4%)	15 (32.6%)		0.40 (0.08, 2.06)	

[1] Upper arm lateral cutis, [2] upper arm lateral subcutis, [3] upper arm medial cutis, [4] upper arm medial subcutis, [5] forearm lateral cutis, [6] forearm lateral subcutis, [7] forearm medial cutis, [8] forearm medial subcutis, [9] hand cutis, [10] hand subcutis, [11] International Society of Lymphology classification, [12] International Society of Lymphology classification Stage 0, [13] International Society of Lymphology classification system, [14] odds ratios.

3.4. Factors Associated with Lymphedema Classified According to Relative Volume Change ≥ 10%

In the univariate analysis, significantly greater measurements at several points were identified, specifically UaMC ($p = <0.001$) and UaLC ($p = 0.028$) regions, as well as in FaMC ($p = <0.001$), FaMSc ($p = 0.007$), and FaLC ($p = 0.009$) regions in participants with RVC ≥ 10%. Moreover, increased echogenicity values were found more frequently in individuals with RVC ≥ 10% ($p = 0.001$).

A multivariable logistic regression analysis was conducted with RVC ≥ 10% as the dependent variable, and UaMs, UaMSc, FaMC, FaMSc, and arm echogenicity as independent variables. The logistic regression model was statistically significant ($p < 0.001$, Nagelkerke $R^2 = 0.575$, accuracy = 0.843). A multivariate analysis model revealed statistical significance for only one variable: FaMS (OR 1.3 (95% CI: (0.99, 1.71), $p = 0.063$)). Specifically, as the interlimb skin thickness increased at the FaMC, the likelihood of an interlimb RVC ≥ 10% also increased (Table 5, Supplementary Materials: Figure S2).

Table 5. Factors associated with lymphedema are classified according to interlimb relative volume change ≥ 10%.

	RVC % [11]		Univariate Model	Multivariable Model	
Variable	<10%	≥10%	*p*-Value	OR (95% C.I)	*p*-Value
UaLC [1], median (IQR)	2.0 (3.0)	3.0 (10.0)	0.028	1.01 (0.93, 1.09)	0.909
UaLSc [2], median (IQR)	9.0 (17.0)	13.0 (22.0)	0.083		
UaMC [3], median (IQR)	2.0 (2.0)	4.0 (4.0)	<0.001	1.14 (0.88, 1.48)	0.316
UaMSc [4], median (IQR)	18.0 (19.0)	24.0 (44.0)	0.211		
FaLC [5], median (IQR)	1.0 (1.0)	2.0 (4.0)	0.009	1.42 (0.86, 2.34)	0.175
FaLSc [6], median (IQR)	6.0 (8.0)	7.0 (15.0)	0.215		
FaMC [7], median (IQR)	1.0 (1.0)	7.0 (8.0)	<0.001	1.3 (0.99, 1.71)	0.064
FaMSc [8], median (IQR)	6.0 (9.0)	13.0 (45.0)	0.007	1.02 (0.97, 1.07)	0.383
HC [9], median (IQR)	13.0 (7.0)	12.0 (9.0)	0.158		
HSc [10], median (IQR)	2.0 (3.0)	3.0 (8.0)	0.534		
Arm echogenicity category n (%)					
Increased echogenicity	10 (20.4%)	14 (66.7%)	<0.001	reference	0.856
Normal echogenitechogenicity	39 (79.6%)	7 (33.3%)		0.851 (0.15, 4.84)	

[1] Upper arm lateral skin, [2] upper arm lateral subcutis, [3] upper arm medial skin, [4] upper arm medial subcutis, [5] forearm lateral skin, [6] forearm lateral subcutis, [7] forearm medial skin, [8] forearm medial subcutis, [9] hand skin, [10] hand subcutis, [11] relative volume change.

3.5. Factors Associated with Lymphedema Classified According to Relative Volume Change ≥ 5%

In the univariate analysis, significantly greater measurements at several points were identified, specifically the UaMC ($p = 0.014$) and UaMSc ($p = 0.032$) regions, as well as at the FaMC ($p = 0.007$), FaFaMSc ($p = 0.006$), and FaFaLSc ($p = 0.029$) regions in participants with RVC ≥ 5% LE. Moreover, increased echogenicity values were found more frequently in individuals with RVC ≥ 5% LE ($p = 0.007$).

To reduce the risk of overfitting given the limited number of outcome events, LASSO regression with 10-fold cross-validation was used for variable selection. All candidate predictors (UaMC, UaMSc, FaLSc, FaMC, FaMSc, and arm echogenicity) were retained. These variables were then included in an age-adjusted multivariable logistic regression model with RVC ≥ 5% as the dependent variable. The model demonstrated good fit (Hosmer–Lemeshow $p = 0.45$), strong discriminative ability (AUC = 0.8), and explained a substantial proportion of variance (Nagelkerke $R^2 = 0.516$). Internal validation using 1000 bootstrap resamples confirmed the robustness and stability of coefficient estimates.

In the final model, only one variable remained statistically significant: UaMC (OR = 1.49, 95% CI: 1.01–2.21, $p = 0.047$). Specifically, increased interlimb skin thickness at the UaMC region was associated with higher odds of exhibiting an interlimb volume difference ≥ 5% (Table 6, Supplementary Materials: Figure S3).

Due to sample size constraints, variables such as BMI, radiotherapy, and axillary surgery type, although clinically relevant, were not included in the multivariate model. However, to address potential concerns about confounding, we conducted a sensitivity analysis by adding each of these variables individually into the model. The results showed no meaningful changes in the odds ratios (ORs) or *p*-values, indicating that these factors

did not substantially confound the observed associations. The results of this analysis are provided in the Supplementary Materials (Table S1).

Table 6. Multivariate logistic regression analysis for the prediction of lymphedema relative volume change ≥ 5%.

	RVC % [11]		Univariate Model	Multivariable Model	
Variable	<5%	≥5%	*p*-Value	OR (95% C.I)	*p*-Value
UaLC [1], median (IQR)	2.0 (2.75)	3.0 (4.0)	0.174		
UaLSc [2], median (IQR)	11.5 (16.75)	11.0 (19.0)	0.409		
UaMC [3], median (IQR)	1.5 (1.0)	3.0 (4.25)	0.014	1.49 (1.01, 2.21)	0.047
UaMSc [4], median (IQR)	14.0 (14.75)	22.0 (36.25)	0.032	1.01 (0.98, 1.05)	0.408
FaLC [5], median (IQR)	2.0 (1.0)	1.5 (3.0)	0.578		
FaLSc [6], median (IQR)	5.0 (7.75)	7.0 (12.0)	0.029	1.09 (0.99, 1.21)	0.087
FaMC [7], median (IQR)	1.0(1.0)	2.0 (6.25)	0.007	1.23 (0.87, 1.73)	0.238
FaMSc [8], median (IQR)	5.0 (5.75)	12.5 (31.0)	0.006	1.03 (0.97, 1.19)	0.329
HC [9], median (IQR)	12.0 (7.0)	13.0 (9.0)	0.934		
HSc [10], median (IQR)	2.0 (2.0)	2.0 (3.75)	1		
Arm echogenicity category n (%)					
Increased echogenicity	5 (20.8%)	19 (79.2%)	0.007	Reference	0.673
Normal echogenicity	25 (54.3%)	21 (45.7%)		0.71 (0.15, 3.48)	

[1] Upper arm lateral skin, [2] upper arm lateral subcutis, [3] upper arm medial skin, [4] upper arm medial subcutis, [5] forearm lateral skin, [6] forearm lateral subcutis, [7] forearm medial skin, [8] forearm medial subcutis, [9] hand skin, [10] hand subcutis, [11] relative volume change.

4. Discussion

This study highlights the potential, simplicity, and clinical applicability of ultrasound-based cutaneous thickness measurements in the medial upper arm region as an effective tool for detecting subclinical BCRL. Based on the results of our study, we firmly believe that US has the potential to differentiate between patients who require early intervention and those suitable for preventive follow-up programs. Multivariate analysis enabled us to control potentially confounding variables and provided insights into the relative impact of individual clinical and ultrasound parameters.

A key finding of this study was a significant association between increased cutis thickness in the medial upper arm region and interlimb volume difference (OR 1.49 (95% CI: (1.01, 2.21), $p = 0.047$)), even when lower volume-based thresholds were considered (RVC ≥ 5%). Our research has highlighted the medial upper arm region as potentially significant, a critical anatomical site for early identification of tissue changes, with increased cutaneous thickness emerging as a particularly sensitive marker for early BCRL detection (Table 6). In contrast, subcutaneous thickness and echogenicity were less sensitive ultrasound measures for detecting early BCRL; they appear to be more indicative of advanced BCRL stages (Tables 4 and 5) [32,43,51].

Furthermore, this distribution pattern aligns with patients' subjective reports in previous research of mild fullness or heaviness in the upper arm, even in the absence of overt swelling [16,18,23,61,62]. Stout et al. proposed that the earliest signs of LE appear in superficial tissues adjacent to muscles, particularly in the forearm and distal upper arm, with localized soft tissue changes around the elbow preceding significant limb volume

increases [14]. Another confirmation of our upper arm medial region finding (Table 6) aligns with anatomical studies indicating that the medial upper arm lymphatic pathway drains directly into axillary lymph nodes, which are commonly affected by surgical removal or radiation therapy [63,64]. Consequently, Friedman et al. described a fluid accumulation pattern predisposed to occur primarily in the posterior distal upper arm (triceps region) and the adjacent medial arm, designating it as a potentially important anatomical site for early BCRL detection [64]. We presume that the lack of statistical significance of lateral arm region measurements in this study lies in the fact that the lateral lymphatic pathways remain unaffected, as they bypass the axilla and serve as a compensatory route for lymphatic drainage following axillary lymph node dissection described by Johnson et al. [63].

Additionally, Johansson et al. detected tissue dielectric constant measurements of highly localized edema in the upper arm, even when total arm volume remained within normal limits [65]. The above-presented anatomical and volume-based studies give insight into possible BCRL location and are consistent with our results [14,62–65].

Our primary finding contrasts with scarce previous ultrasound studies, which did not identify the medial region of the upper arm as a significant site for BCRL detection. Instead, they focused on forearm anatomical sites [3,29,35,48–50]. Studies by Devoogdt et al. and Polat et al., for example, highlighted that changes in tissue thickness and stiffness of the forearm reflect latent lymphedema [46,48]. Our findings suggest that earlier studies may have overlooked early signs of LE by underestimating the proximal tissue changes pattern in BCRL patients by underestimating the pattern of proximal tissue changes in BCRL patients. However, across these studies, the overall sensitivity of US findings for subclinical lymphedema detection has been modest, and conclusions were inconsistent. The detection of early lymphedema tissue changes in the upper arm implies that BCRL may not universally begin in the forearm, as suggested in previous latent lymphedema US studies [48]. Instead, as indicated in our research, more proximal arm tissues could be involved earlier than previously believed.

We believe that the discrepancy in the identification of anatomical sites for early BCRL detection between our study and previous studies lies in the use of different BCRL diagnostic thresholds. The most commonly accepted volume criterion to diagnose BCRL still is RVC $\geq$ 10%, although it has already been demonstrated that this threshold may fail to capture subclinical or early BCRL cases, potentially classifying patients as not having BCRL, thereby delaying timely diagnosis and intervention that could prevent disease progression [13,19,23,27,28,39,62,66].

When a conservative, volume-based clinical definition of lymphedema was applied in our cohort, ultrasonography identified the medial forearm as a crucial anatomical site for BCRL identification. Specifically, using relative volume change $\geq$ 10% to define BCRL, we observed that a positive ultrasound finding at the medial forearm was associated with higher odds of lymphedema (OR 1.3, 95% CI 0.99–1.71, p = 0.063; see Table 5). Furthermore, we detected the same forearm measuring site when applying ISL stage classification (OR 1.71, 95% CI: 1.02–2.86, p = 0.041, see Table 4). Previous authors have also highlighted inconsistencies and limitations in detecting early BCRL using traditional diagnostic approaches [46,47,55].

The prominence of the medial forearm observed in our US findings among participants with more advanced lymphedema aligns with recent anatomical insights into lymphatic drainage patterns, which differ between the medial and lateral forearm regions [64]. Anatomical studies suggest variations in lateral lymphatic bundle length, which drains towards the deltoid-pectoral and supraclavicular lymph nodes, may leave the medial forearm without an adequate drainage route, leading to lymphatic fluid accumulation [63,64]. Ad-

ditionally, the medial aspect of the forearm may be more prone to fluid stasis in advanced stages of BCRL due to gravitational effects [31,32].

In conclusion, our findings highlight the limitations of traditional volume-based criteria in detecting subclinical BCRL and underscore the value of ultrasound-based cutaneous thickness measurements as a sensitive and complementary tool for early diagnosis, enabling timely intervention and potentially preventing disease progression. Additionally, in the absence of a universally accepted gold standard for detecting subclinical BCRL, this study compared US to commonly used reference methods, ISL staging, and RVC thresholds of 5% and 10% [10,19,67]. These methods are imperfect reference standards, which may introduce bias and affect sensitivity and specificity estimates by misclassifying disease status, and thus distorting the true performance of ultrasound [68]. The 5% RVC threshold is increasingly favored, supported by expert consensus and evidence showing that early intervention at this level can prevent progression to chronic lymphedema [9,55,69]. This aligns with modern BCRL management's preventive focus, whereas the more conservative 10% threshold may delay timely treatment [17,67]. Thus, the 5% RVC threshold is advocated as the primary benchmark for early detection.

Our study extends the current understanding of ultrasound's diagnostic utility in BCRL by highlighting a previously under-recognized anatomical site, the medial upper arm, for early detection. It also reaffirms the importance of forearm assessments while providing new insights into how lymphedema might spread in the limb. These findings underscore the need for further investigation into the spatiotemporal development of BCRL, which could inform more effective surveillance strategies and tailored interventions for at-risk patients.

4.1. Limitations of the Study

A key limitation of our study is its cross-sectional design, which limits the ability to assess the temporal progression of BCRL and the predictive value of our ultrasound findings. Additionally, our study's retrospective and single-centre nature may have introduced selection bias and limited the ability to determine causal inference. Future multicentre, prospective longitudinal studies should enrol breast cancer patients before the initiation of cancer treatment and follow them over time to evaluate whether subclinical changes in subcutaneous tissue thickness detected by ultrasound can predict the onset and progression of BCRL.

Since our institution is a tertiary referral centre, the diagnostic accuracy reported in this study may have been overestimated because of potential disease spectrum bias. However, our centre also serves as the sole facility within the county providing specialized lymphedema diagnosis and management. Consequently, all breast cancer survivors in the region requiring such services are routinely referred to our clinic. This dual role mitigates the risk of disease spectrum bias and enhances the generalizability of our findings to the broader population of breast cancer survivors in comparable healthcare settings. Additionally, the absence of preoperative baseline measurements restricted the ability to determine the exact magnitude of post-treatment changes or differentiate between pre-existing anatomical variations and LE-related alterations. However, this limitation was mitigated by including only patients with unilateral breast cancer, allowing the contralateral unaffected limb to serve as an internal control for each patient. The lack of follow-up assessments further limits the evaluation of the predictive value of ultrasonographic markers over time and their role in tracking disease progression.

Finally, although a 20 MHz frequency ultrasound probe offers greater sensitivity for superficial skin structures, we utilized a 9–12 MHz frequency probe to balance resolution with deeper tissue penetration. It may have limited detection of subtle dermal–epidermal

changes but is more suitable for evaluating advanced lymphedema. We believe that the 9–12 MHz probe allowed consistent assessment of key dermal and subcutaneous features and reflects real-world constraints, supporting the applicability of our findings across diverse clinical settings.

4.2. Strengths of the Study

Compared to similar studies, this research included a relatively large sample size, enhancing statistical power and generalizability. Multiple measurements of cutaneous and subcutaneous tissue thickness and echogenicity across different anatomical regions provided a detailed and region-specific evaluation of LE-related changes. To ensure measurement reliability, ultrasonographic assessments demonstrated high inter- and intra-rater consistency, with all imaging performed by a single experienced radiologist blinded to surgical history, minimizing bias. Standardized protocols were also applied to circumference measurements, ensuring consistency in LE classification. Unlike studies relying solely on absolute volume differences, this research accounted for relative volume changes, such as weight fluctuations, improving diagnostic accuracy. Additionally, by employing multivariate analysis, this study simultaneously evaluated multiple factors, identifying independent predictors of LE progression while controlling for potential confounding variables. Integrating clinical and ultrasonographic parameters strengthened the precision and reliability of interpreting complex interactions related to LE development and progression.

Overall, this study's strengths contribute to the robustness of our findings, while the acknowledged limitations highlight areas for future research to improve the diagnostic and prognostic utility of ultrasonography in BCRL assessment.

5. Conclusions

This is one of the most extensive studies performed, underscoring the potential of ultrasound as an effective tool for the early detection and monitoring of BCRL.

Among BCRL patients with low volume changes, conventional diagnostic methods used in clinical practice, such as ISL staging, circumference, and volume measurements, are often insufficiently sensitive to distinguish patients who require early intervention from those suitable for preventive follow-up programs. These limitations allow disease progression, significantly impacting patients' physical and psychological well-being.

Our findings identified the medial upper arm region as a potentially important anatomical site for the early detection of BCRL-related tissue changes. This region has not been previously emphasized in early detection US studies. Specifically, increased cutaneous thickness in this area emerged as a sensitive marker for detecting early signs of the disease, even among participants with minimal limb volume changes. However, we recognize that this association, while statistically significant (OR 1.49), is modest, and the cross-sectional design precludes conclusions about causality. In contrast, subcutaneous thickness and echogenicity appeared less predictive of early-stage BCRL but may hold greater relevance in more advanced stages. This distinction underscores the clinical significance of cutaneous thickness measurements as a potential ultrasound parameter for timely identification and intervention before significant volume changes occur. Despite the promising diagnostic utility of ultrasound, the lack of standardized imaging protocols and echogenicity grading remains a challenge. Future research should employ longitudinal designs to validate predictive values of ultrasonographic findings and to monitor temporal changes in tissue characteristics associated with BCRL progression. Additionally, efforts should focus on developing and validating standardized US protocols and establishing threshold values for early detection to improve clinical decision making and optimize patient care.

Supplementary Materials: The following supporting information can be downloaded at: https://www.mdpi.com/article/10.3390/biomedicines13061396/s1, Figure S1: Forest plot showing summary results (Odds ratios (OR) and 95% confidence intervals (95% C.I) of multivariable regression analysis for the prediction of ISL stage. Multivariable model analysis revealed statistical significance for two variables: UaMSc and FaMC measuring points (*UaMC upper arm medial cutis, *UaMSc upper arm medial subcutis, *FaMC forearm medial cutis, *FaMSc forearm medial subcutis). Specifically, as the interlimb skin thickness increased in the FaMC and UaMSc regions, the likelihood of a higher ISL stage also increased (Table 4); Figure S2: Forest plot showing summary results (Odds ratios (OR) and 95% confidence intervals (95% C.I) of multivariable regression analysis for the prediction of RVC 10%. Multivariable model analysis revealed statistical significance for one variable: FaMC measuring point (*UaMC upper arm medial cutis, *UaMSc upper arm medial subcutis, *FaMC forearm medial cutis, *FaMSc forearm medial subcutis). Specifically, as the interlimb skin thickness increased in the FaMC region, the likelihood of RVC 10% also increased (Table 5). Figure S3: Forest plot showing summary results (Odds ratios (OR) and 95% confidence intervals (95% C.I) of multivariable regression analysis for the prediction of RVC 5%. Multivariable model analysis revealed statistical significance for one variable: UaMC measuring point (*UaMC upper arm medial cutis, *UaMSc upper arm medial subcutis, *FaMC forearm medial cutis, *FaMSc forearm medial subcutis). Specifically, as the interlimb skin thickness increased in the UaMC region, the likelihood of RVC 5% also increased (Table 6). Table S1: Results of the sensitivity analysis for the multivariate logistic regression analysis for the prediction of lymphedema relative volume change $\geq$ 5%. We included each of the variables—BMI, radiotherapy, and axillary surgery type—individually in the model

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Informed Consent Statement: Prior to enrolment in the study, all participating women were informed about the nature of the study, and written informed consent was obtained.

Data Availability Statement: The data presented in this study are available on request from the corresponding author.

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Abbreviations

The following abbreviations are used in this manuscript:

LE	Lymphedema
BCRL	Breast cancer-related lymphedema
ISL	International Society of Lymphology

US	Ultrasonography
RVC	Relative volume change
ICC	Interclass correlation coefficient
SD	Standard deviation
IQR	Interquartile range
CI	Confidence intervals
UaLC	Upper arm lateral cutis
UaLSc	Upper arm lateral subcutis
UaMC	Upper arm medial cutis
UaMSc	Upper arm medial subcutis
FaLC	Forearm lateral cutis
FaLSc	Forearm lateral subcutis
FaMC	Forearm medial cutis
FaMSc	Forearm medial subcutis
HC	Hand cutis
HSc	Hand subcutis
ALND	Axillary lymph node dissection
MHz	Megahertz

Appendix A

Table A1. Ultrasonography cutis and subcutis thickness reliability testing.

Measuring Site	ICC (95% C.I.)	ICC (95% C.I.)
	Inter-Rater Reliability Researcher 1 and Researcher 2	**Inter-Rater Reliability Researcher 1 and Researcher 2**
UaLC [1]	0.890 (0.75, 0.96)	0.859 (0.68, 0.94)
UaLSc [2]	0.870 (0.49, 0.97)	0.91 (0.79, 0.96)
UaMC [3]	0.848 (0.66, 0.93)	0.910 (0.79, 0.96)
UaMSc [4]	0.997 (0.99, 0.99)	0.889 (0.746, 0.954)
FaLC [5]	0.963 (0.91, 0.99)	0.935 (0.85, 0,97)
FaLSc [6]	0.830 (0.63, 0.93)	0.814 (0.60, 0.92)
FaMC [7]	0.935 (0.85, 0.97)	0.954 (0.89, 0.98)
FaMSc [8]	0.978 (0.95, 0.99)	0.978 (0.95, 0.99)
HC [9]	0.979 (0.95, 0.99)	0.964 (0.91, 0.99)
HSc [10]	0.88 (0.73, 0.95)	0.725 (0.43, 0.88)
	<0.5 poor **0.5–0.75 good** **0.75–0.9 good** **>0.9 excellent**	

[1] Upper arm lateral skin, [2] upper arm lateral subcutis, [3] upper arm medial skin, [4] upper arm medial subcutis, [5] forearm lateral skin, [6] forearm lateral subcutis, [7] forearm medial skin, [8] forearm medial subcutis, [9] hand skin, [10] hand subcutis.

Table A2. Limb centimetre measurements reliability testing.

Measuring Site	ICC (95% C.I.)	ICC (95% C.I.)
	Inter-Rater Reliability Researcher 1 and Researcher 1	**Inter-Rater Reliability Researcher 1 and Researcher 1**
Measuring point 0	0.999 (0.99, 0.99)	0.999 (0.99, 0.99)
Measuring point 1	1.00 (0.99, 1.00)	0.999 (0.99, 1.00)
Measuring point 2	1.00 (0.99, 1.00)	0.651 (0.41,0.81)
Measuring point 3	1.00 (0.99,1.00)	1.00 (0.99, 1.00)

References

1. Földi, M. On the pathophysiology of arm lymphedema after treatment for breast cancer. *Lymphology* **1995**, *28*, 151–158. [PubMed]
2. Ricci, V.; Ricci, C.; Gervasoni, F.; Andreoli, A.; Özçakar, L. From histo-anatomy to sonography in lymphedema: EURO-MUSCULUS/USPRM approach. *Eur. J. Phys. Rehabil. Med.* **2022**, *58*, 108–117. [CrossRef] [PubMed]
3. Mander, A.; Venosi, S.; Menegatti, E.; Byung-Boong, L.; Neuhardt, D.; Maietti, E.; Gianesini, S. Upper limb secondary lymphedema ultrasound mapping and characterization. *Int. Angiol.* **2019**, *38*, 334–342. [CrossRef]
4. Bok, S.K.; Jeon, Y.; Hwang, P.S. Ultrasonographic Evaluation of the Effects of Progressive Resistive Exercise in Breast Cancer-Related Lymphedema. *Lymphat. Res. Biol.* **2016**, *14*, 18–24. [CrossRef] [PubMed]
5. Paskett, E.D.; Dean, J.A.; Oliveri, J.M.; Harrop, J.P. Cancer-related lymphedema risk factors, diagnosis, treatment, and impact: A review. *J. Clin. Oncol.* **2012**, *30*, 3726–3733. [CrossRef]
6. DiSipio, T.; Rye, S.; Newman, B.; Hayes, S. Incidence of unilateral arm lymphoedema after breast cancer: A systematic review and meta-analysis. *Lancet Oncol.* **2013**, *14*, 500–515. [CrossRef]
7. Torgbenu, E.; Luckett, T.; Buhagiar, M.A.; Chang, S.; Phillips, J.L. Prevalence and incidence of cancer related lymphedema in low and middle-income countries: A systematic review and meta-analysis. *BMC Cancer* **2020**, *20*, 604. [CrossRef]
8. Skjødt Rafn, B.; Jensen, S.; Bjerre, E.D.; Wittenkamp, M.C.; Benjaminsen, K.; Christensen, L.P.; Flyger, H.; Christiansen, P.; Johansen, C. Prospective surveillance for breast cancer-related lymphedema (PROTECT). *Acta Oncol.* **2023**, *62*, 808–813. [CrossRef]
9. Stout, N.L.; Binkley, J.M.; Schmitz, K.H.; Andrews, K.; Hayes, S.C.; Campbell, K.L.; McNeely, M.L.; Soballe, P.W.; Berger, A.M.; Cheville, A.L.; et al. A prospective surveillance model for rehabilitation for women with breast cancer. *Cancer* **2012**, *118*, 2191–2200. [CrossRef]
10. Executive Committee of the International Society of Lymphology. The diagnosis and treatment of peripheral lymphedema: 2020 Consensus Document of the International Society of Lymphology. *Lymphology* **2020**, *53*, 3–19.
11. Hayes, S.; Cornish, B.; Newman, B. Preoperative assessment enables the early detection and successful treatment of lymphedema. *Cancer* **2010**, *116*, 260. [CrossRef] [PubMed]
12. Stanton, A.W.; Badger, C.; Sitzia, J. Non-invasive assessment of the lymphedematous limb. *Lymphology* **2000**, *33*, 122–135. [PubMed]
13. Smoot, B.J.; Wong, J.F.; Dodd, M.J. Comparison of diagnostic accuracy of clinical measures of breast cancer-related lymphedema: Area under the curve. *Arch. Phys. Med. Rehabil.* **2011**, *92*, 603–610. [CrossRef]
14. Stout, N.L.; Pfalzer, L.A.; Levy, E.; McGarvey, C.; Springer, B.; Gerber, L.H.; Soballe, P. Segmental limb volume change as a predictor of the onset of lymphedema in women with early breast cancer. *PM R* **2011**, *3*, 1098–1105. [CrossRef]
15. Tassenoy, A.; De Mey, J.; De Ridder, F.; Van Schuerbeeck, P.; Vanderhasselt, T.; Lamote, J.; Lievens, P. Postmastectomy lymphoedema: Different patterns of fluid distribution visualised by ultrasound imaging compared with magnetic resonance imaging. *Physiotherapy* **2011**, *97*, 234–243. [CrossRef]
16. Ridner, S.H.; Montgomery, L.D.; Hepworth, J.T.; Stewart, B.R.; Armer, J.M. Comparison of upper limb volume measurement techniques and arm symptoms between healthy volunteers and individuals with known lymphedema. *Lymphology* **2007**, *40*, 35–46. [PubMed]
17. Specht, M.C.; Miller, C.L.; Russell, T.A.; Horick, N.; Skolny, M.N.; O'Toole, J.A.; Jammallo, L.S.; Niemierko, A.; Sadek, B.T.; Shenouda, M.N.; et al. Defining a threshold for intervention in breast cancer-related lymphedema: What level of arm volume increase predicts progression? *Breast Cancer Res. Treat.* **2013**, *140*, 485–494. [CrossRef]
18. Yanardağ, C.H.; Çürük, G.N.; Karayurt, Ö. Effects of selfcare and selected factors on the quality of life in women with breast cancer-related lymphedema. *Support. Care Cancer* **2022**, *31*, 22. [CrossRef]
19. Levenhagen, K.; Davies, C.; Perdomo, M.; Ryans, K.; Gilchrist, L. Diagnosis of Upper Quadrant Lymphedema Secondary to Cancer: Clinical Practice Guideline from the Oncology Section of the American Physical Therapy Association. *Phys. Ther.* **2017**, *97*, 729–745. [CrossRef]

20. Boyages, J.; Vicini, F.A.; Shah, C.; Koelmeyer, L.A.; Nelms, J.A.; Ridner, S.H. The Risk of Subclinical Breast Cancer-Related Lymphedema by the Extent of Axillary Surgery and Regional Node Irradiation: A Randomized Controlled Trial. *Int. J. Radiat. Oncol. Biol. Phys.* **2021**, *109*, 987–997. [CrossRef]
21. Fu, M.R.; Axelrod, D.; Cleland, C.M.; Qiu, Z.; Guth, A.A.; Kleinman, R.; Scagliola, J.; Haber, J. Symptom report in detecting breast cancer-related lymphedema. *Breast Cancer* **2015**, *7*, 345–352. [CrossRef] [PubMed]
22. Gençay Can, A.; Ekşioğlu, E.; Çakçı, F.A. Early Detection and Treatment of Subclinical Lymphedema in Patients with Breast Cancer. *Lymphat. Res. Biol.* **2019**, *17*, 368–373. [CrossRef] [PubMed]
23. Czerniec, S.A.; Ward, L.C.; Refshauge, K.M.; Beith, J.; Lee, M.J.; York, S.; Kilbreath, S.L. Assessment of breast cancer-related arm lymphedema—Comparison of physical measurement methods and self-report. *Cancer Investig.* **2010**, *28*, 54–62. [CrossRef]
24. Michelotti, A.; Invernizzi, M.; Lopez, G.; Lorenzini, D.; Nesa, F.; De Sire, A.; Fusco, N. Tackling the diversity of breast cancer related lymphedema: Perspectives on diagnosis, risk assessment, and clinical management. *Breast* **2019**, *44*, 15–23. [CrossRef]
25. Hayes, S.; Cornish, B.; Newman, B. Comparison of methods to diagnose lymphoedema among breast cancer survivors: 6-month follow-up. *Breast Cancer Res. Treat.* **2005**, *89*, 221–226. [CrossRef]
26. Ancukiewicz, M.; Russell, T.A.; Otoole, J.; Specht, M.; Singer, M.; Kelada, A.; Murphy, C.D.; Pogachar, J.; Gioioso, V.; Patel, M.; et al. Standardized method for quantification of developing lymphedema in patients treated for breast cancer. *Int. J. Radiat. Oncol. Biol. Phys.* **2011**, *79*, 1436–1443. [CrossRef]
27. Armer, J.M.; Stewart, B.R. A comparison of four diagnostic criteria for lymphedema in a post-breast cancer population. *Lymphat. Res. Biol.* **2005**, *3*, 208–217. [CrossRef] [PubMed]
28. Armer, J.M. The problem of post-breast cancer lymphedema: Impact and measurement issues. *Cancer Investig.* **2005**, *23*, 76–83. [CrossRef]
29. Choi, Y.H.; Seo, K.S. Correlation among bioimpedance analysis, sonographic and circumferential measurement in assessment of breast cancer-related arm lymphedema. *Lymphology* **2014**, *47*, 123–133.
30. Özçakar, L.; Kara, M.; Chang, K.V.; Çarl, A.B.; Akkaya, N.; Tok, F.; Chen, W.S.; Wang, T.G.; Tekin, L.; Ulaşl, A.M.; et al. Nineteen reasons why physiatrists should do musculoskeletal ultrasound: EURO-MUSCULUS/USPRM recommendations. *Am. J. Phys. Med. Rehabil.* **2015**, *94*, e45–e49. [CrossRef]
31. Suehiro, K.; Morikage, N.; Murakami, M.; Yamashita, O.; Samura, M.; Hamano, K. Significance of ultrasound examination of skin and subcutaneous tissue in secondary lower extremity lymphedema. *Ann. Vasc. Dis.* **2013**, *6*, 180–188. [CrossRef] [PubMed]
32. Suehiro, K.; Morikage, N.; Yamashita, O.; Harada, T.; Samura, M.; Takeuchi, Y.; Mizoguchi, T.; Nakamura, K.; Hamano, K. Skin and Subcutaneous Tissue Ultrasonography Features in Breast Cancer-Related Lymphedema. *Ann. Vasc. Dis.* **2016**, *9*, 312–316. [CrossRef] [PubMed]
33. Suehiro, K.; Yamamoto, S.; Honda, S.; Morikage, N.; Harada, E.; Takemoto, Y.; Nagano, H.; Hamano, K. Perioperative variations in indices derived from noninvasive assessments to detect postmastectomy lymphedema. *J. Vasc. Surg. Venous Lymphat. Disord.* **2019**, *7*, 562–569. [CrossRef] [PubMed]
34. Giray, E.; Yagci, I. Diagnostic accuracy of interlimb differences of ultrasonographic subcutaneous tissue thickness measurements in breast cancer-related arm lymphedema. *Lymphology* **2019**, *52*, 1–10. [CrossRef]
35. Mellor, R.H.; Bush, N.L.; Stanton, A.W.; Bamber, J.C.; Levick, J.R.; Mortimer, P.S. Dual-frequency ultrasound examination of skin and subcutis thickness in breast cancer-related lymphedema. *Breast J.* **2004**, *10*, 496–503. [CrossRef]
36. van der Veen, P.; Vermeiren, K.; Von Kemp, K.; Lamote, J.; Sacre, R.; Lievens, P. A key to understanding postoperative lymphoedema: A study on the evolution and consistency of oedema of the arm using ultrasound imaging. *Breast* **2001**, *10*, 225–230. [CrossRef]
37. Yang, E.J.; Kim, S.Y.; Lee, W.H.; Lim, J.Y.; Lee, J. Diagnostic Accuracy of Clinical Measures Considering Segmental Tissue Composition and Volume Changes of Breast Cancer-Related Lymphedema. *Lymphat. Res. Biol.* **2018**, *16*, 368–376. [CrossRef]
38. Johnson, K.C.; DeSarno, M.; Ashikaga, T.; Dee, J.; Henry, S.M. Ultrasound and Clinical Measures for Lymphedema. *Lymphat. Res. Biol.* **2016**, *14*, 8–17. [CrossRef]
39. Sanderson, J.; Tuttle, N.; Box, R.; Reul-Hirche, H.; Laakso, E.L. Localised Objective Characterisation Assessment of Lymphoedema (LOCAL): Using High-Frequency Ultrasound, Bioelectrical Impedance Spectroscopy and Volume to Evaluate Superficial Tissue Composition. *Diagnostics* **2024**, *14*, 1616. [CrossRef]
40. Vargo, M.; Aldrich, M.; Donahue, P.; Iker, E.; Koelmeyer, L.; Crescenzi, R.; Cheville, A. Current diagnostic and quantitative techniques in the field of lymphedema management: A critical review. *Med. Oncol.* **2024**, *41*, 241. [CrossRef]
41. Mayrovitz, H.N. Medical Applications of Skin Tissue Dielectric Constant Measurements. *Cureus* **2023**, *15*, e50531. [CrossRef] [PubMed]
42. Jeon, Y.; Beom, J.; Ahn, S.; Bok, S.K. Ultrasonographic Evaluation of Breast Cancer-related Lymphedema. *J. Vis. Exp.* **2017**, *42*, e54996. [CrossRef]
43. Park, J.Y.; Jeon, J.Y.; Cha, S. Ultrasonographic features of the skin and subcutis: Correlations with the severity of breast cancer-related lymphedema. *Ultrasonography* **2024**, *43*, 284–293. [CrossRef]

44. Duan, L.; Zhao, L.; Liu, Y.; Zhang, Y.; Zheng, W.; Yu, X.; Liu, H.; Li, Z.; Peng, Z.; Li, X. Neuralgic amyotrophy: Sensitivity and specificity of magnetic resonance neurography in diagnosis: A retrospective study. *Medicine* **2023**, *102*, e35527. [CrossRef] [PubMed]
45. Forte, A.J.; Huayllani, M.T.; Boczar, D.; Cinotto, G.; McLaughlin, S.A. Ultrasound Elastography Use in Lower Extremity Lymphedema: A Systematic Review of the Literature. *Cureus* **2019**, *11*, e5578. [CrossRef]
46. Devoogdt, N.; Pans, S.; De Groef, A.; Geraerts, I.; Christiaens, M.R.; Neven, P.; Vergote, I.; Van Kampen, M. Postoperative evolution of thickness and echogenicity of cutis and subcutis of patients with and without breast cancer-related lymphedema. *Lymphat. Res. Biol.* **2014**, *12*, 23–31. [CrossRef]
47. de Rezende, L.F.; Piloni, J.P.M.; Kempa, V.L.; Silva, J.F.R.; Vilas Boas, V.F.; Carvalho, R.L.; Marx, Â.G. Ultrasonography as an instrument to evaluate lymphedema secondary to breast cancer: Systematic review. *J. Vasc. Bras.* **2023**, *22*, e20220144. [CrossRef] [PubMed]
48. Polat, A.V.; Ozturk, M.; Polat, A.K.; Karabacak, U.; Bekci, T.; Murat, N. Efficacy of Ultrasound and Shear Wave Elastography for the Diagnosis of Breast Cancer-Related Lymphedema. *J. Ultrasound Med.* **2020**, *39*, 795–803. [CrossRef]
49. Giray, E.; Yağcı, İ. Interrater and Intrarater Reliability of Subcutaneous Echogenicity Grade and Subcutaneous Echo-Free Space Grade in Breast Cancer-Related Lymphedema. *Lymphat. Res. Biol.* **2019**, *17*, 518–524. [CrossRef]
50. Kim, S.Y.; Lee, C.H.; Heo, S.J.; Moon, M.H. The Clinical Usefulness of Lymphedema Measurement Technique Using Ultrasound. *Lymphat. Res. Biol.* **2021**, *19*, 340–346. [CrossRef]
51. Duyur Çakıt, B.; Ayhan, F.F.; Gümrük Aslan, S.; Genç, H. The role of ultrasonography in follow-up of effectiveness of Complex Decongestive Therapy (CDT) in different subgroups of patients with breast cancer-related lymphoedema. *Eur. J. Cancer Care* **2021**, *30*, e13376. [CrossRef] [PubMed]
52. Brunelle, C.L.; Barrio, A.V.; Shaitelman, S.F.; Singhal, D.; Sayegh, H.E.; Taghian, A.G. On "Diagnosis of Upper Quadrant Lymphedema Secondary to Cancer: Clinical Practice Guideline from the Oncology Section of the American Physical Therapy Association." Levenhagen K, Davies C, Perdomo M, Ryans K, Gilchrist L. Phys Ther. 2017;97:729–745. *Phys. Ther.* **2018**, *98*, 277–281. [CrossRef] [PubMed]
53. Taylor, R.; Jayasinghe, U.W.; Koelmeyer, L.; Ung, O.; Boyages, J. Reliability and validity of arm volume measurements for assessment of lymphedema. *Phys. Ther.* **2006**, *86*, 205–214. [CrossRef]
54. Deltombe, T.; Jamart, J.; Recloux, S.; Legrand, C.; Vandenbroeck, N.; Theys, S.; Hanson, P. Reliability and limits of agreement of circumferential, water displacement, and optoelectronic volumetry in the measurement of upper limb lymphedema. *Lymphology* **2007**, *40*, 26–34.
55. Soran, A.; Ozmen, T.; McGuire, K.P.; Diego, E.J.; McAuliffe, P.F.; Bonaventura, M.; Ahrendt, G.M.; DeGore, L.; Johnson, R. The importance of detection of subclinical lymphedema for the prevention of breast cancer-related clinical lymphedema after axillary lymph node dissection; a prospective observational study. *Lymphat. Res. Biol.* **2014**, *12*, 289–294. [CrossRef] [PubMed]
56. Bundred, N.; Foden, P.; Todd, C.; Morris, J.; Watterson, D.; Purushotham, A.; Bramley, M.; Riches, K.; Hodgkiss, T.; Evans, A.; et al. Increases in arm volume predict lymphoedema and quality of life deficits after axillary surgery: A prospective cohort study. *Br. J. Cancer* **2020**, *123*, 17–25. [CrossRef]
57. Stout Gergich, N.L.; Pfalzer, L.A.; McGarvey, C.; Springer, B.; Gerber, L.H.; Soballe, P. Preoperative assessment enables the early diagnosis and successful treatment of lymphedema. *Cancer* **2008**, *112*, 2809–2819. [CrossRef]
58. Togawa, K.; Ma, H.; Smith, A.W.; Neuhouser, M.L.; George, S.M.; Baumgartner, K.B.; McTiernan, A.; Baumgartner, R.; Ballard, R.M.; Bernstein, L. Self-reported symptoms of arm lymphedema and health-related quality of life among female breast cancer survivors. *Sci. Rep.* **2021**, *11*, 10701. [CrossRef]
59. Bosompra, K.; Ashikaga, T.; O'Brien, P.J.; Nelson, L.; Skelly, J. Swelling, numbness, pain, and their relationship to arm function among breast cancer survivors: A disablement process model perspective. *Breast J.* **2002**, *8*, 338–348. [CrossRef]
60. Liu, Y.F.; Liu, J.E.; Zhu, Y.; Mak, Y.W.; Qiu, H.; Liu, L.H.; Yang, S.S.; Chen, S.H. Development and validation of a nomogram to predict the risk of breast cancer-related lymphedema among Chinese breast cancer survivors. *Support. Care Cancer* **2021**, *29*, 5435–5445. [CrossRef]
61. Zhang, X.; Oliveri, J.M.; Paskett, E.D. Features, Predictors, and Treatment of Breast Cancer–Related Lymphedema. *Curr. Breast Cancer Rep.* **2020**, *12*, 244–254. [CrossRef] [PubMed]
62. Brunelle, C.L.; Roberts, S.A.; Horick, N.K.; Gillespie, T.C.; Jacobs, J.M.; Daniell, K.M.; Naoum, G.E.; Taghian, A.G. Integrating Symptoms Into the Diagnostic Criteria for Breast Cancer-Related Lymphedema: Applying Results From a Prospective Surveillance Program. *Phys. Ther.* **2020**, *100*, 2186–2197. [CrossRef]
63. Johnson, A.R.; Bravo, M.G.; James, T.A.; Suami, H.; Lee, B.T.; Singhal, D. The All but Forgotten Mascagni-Sappey Pathway: Learning from Immediate Lymphatic Reconstruction. *J. Reconstr. Microsurg.* **2020**, *36*, 28–31. [CrossRef] [PubMed]
64. Friedman, R.; Lee, C.; Kinney, J.R.; Salehi, B.P.; Kim, G.; Singhal, D.; Tsai, L.L. Fluid Distribution Patterns in Early-Stage Upper Extremity Lymphedema. *Ann. Plast. Surg.* **2023**, *90*, S622–S625. [CrossRef] [PubMed]

65. Johansson, K.; Blom, K.; Nilsson-Wikmar, L.; Brogårdh, C. Early Intervention with a Compression Sleeve in Mild Breast Cancer-Related Arm Lymphedema: A 12-Month Prospective Observational Study. *Cancers* **2023**, *15*, 2674. [CrossRef]
66. Dylke, E.S.; Yee, J.; Ward, L.C.; Foroughi, N.; Kilbreath, S.L. Normative volume difference between the dominant and nondominant upper limbs in healthy older women. *Lymphat. Res. Biol.* **2012**, *10*, 182–188. [CrossRef]
67. Davies, C.; Levenhagen, K.; Ryans, K.; Perdomo, M.; Gilchrist, L. Interventions for Breast Cancer-Related Lymphedema: Clinical Practice Guideline From the Academy of Oncologic Physical Therapy of APTA. *Phys. Ther.* **2020**, *100*, 1163–1179. [CrossRef]
68. Lijmer, J.G.; Mol, B.W.; Heisterkamp, S.; Bonsel, G.J.; Prins, M.H.; van der Meulen, J.H.; Bossuyt, P.M. Empirical evidence of design-related bias in studies of diagnostic tests. *JAMA* **1999**, *282*, 1061–1066. [CrossRef]
69. McLaughlin, S.A.; Brunelle, C.L.; Taghian, A. Breast Cancer-Related Lymphedema: Risk Factors, Screening, Management, and the Impact of Locoregional Treatment. *J. Clin. Oncol.* **2020**, *38*, 2341–2350. [CrossRef]

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Measuring What Matters for Breast Cancer Survivors: Translation, Cross-Cultural Adaptation and Validation of the Croatian Version of Lymphedema Quality of Life Tool-Arm

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Abstract

Background: Breast cancer-related lymphedema is a common long-term complication of breast cancer treatment that affects physical functioning, emotional well-being, and quality of life. Although the Lymphedema Quality of Life Questionnaire-Arm (LYMQoL-Arm) is widely used internationally, no Croatian version has been available. The primary objective of this study was to translate and validate the Lymphedema Quality of Life Questionnaire-Upper Limb-Croatian (LYMQoL-UL-CRO) version and evaluate its psychometric properties. A secondary objective was to examine associations between its scores and the relative volume change (RVC) of the affected limb to assess construct validity further. **Methods:** A retrospective cross-sectional study was conducted in 87 women at least six months post-treatment. The questionnaire was translated using a forward-backward procedure. Participants completed the LYMQoL-UL-CRO, the Short Form-36 Health Survey (SF-36), Pain Intensity Numerical Rating Scale, and underwent clinical examination and limb-volume assessment. Test–retest reliability was assessed in 68 participants after 10 days. Psychometric analyses included internal consistency, intraclass correlation coefficients, measurement error indices, construct and discriminant validity tests, exploratory factor analysis, and evaluation of floor and ceiling effects. **Results:** LYMQoL-UL-CRO domains demonstrated acceptable to strong internal consistency and moderate test–retest reliability, with low measurement error. Strong negative correlations with the SF-36 Physical Component Summary supported construct validity, and participants with RVC $\geq 5\%$ reported worse scores, supporting discriminant validity. Exploratory factor analysis confirmed the original four-factor structure, and no floor or ceiling effects were observed. **Conclusions:** The LYMQoL-UL-CRO is a reliable, valid, and culturally appropriate tool for assessing quality of life in Croatian breast cancer survivors with upper-limb lymphedema.

Keywords: quality of life; breast neoplasms; lymphedema; rehabilitation; patient-reported outcomes; validation

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1. Introduction

Advancements in breast cancer treatment over the past two decades have significantly increased long-term survivorship [1]. Survivorship phase in cancer care continuum, begin-

ning five years after completion of treatment, marks a transition in patient care as oncologic follow-up becomes less frequent, and survivors face late treatment-related toxicities, new comorbidities, and ongoing psychosocial challenges [2].

However, existing clinical practice guidelines largely address short-term side effects, within five years post-treatment. Evidence on outcomes beyond this period remains limited, creating a substantial gap in knowledge and care for long-term survivors [2,3]. This gap leaves long-term survivors without sufficient guidance for managing persistent symptoms, comorbidities, and psychological issues. Long-term breast cancer survivors experience physical symptoms such as fatigue, chronic pain, lymphedema, and sleep disturbance as well as psychological problems such as anxiety and depression, which may negatively impact quality of life (QoL) and may require specialised care [4]. Although guidelines are meant to be updated every three to five years, many fail to incorporate the most recent evidence and recommendations relevant to the long-term survivorship phase. Consequently, research and clinical frameworks still focus mainly on recurrence surveillance and physical outcomes, with less attention to comprehensive survivorship care that supports overall well-being and quality of life [2,5].

Recent literature increasingly supports the view of breast cancer as a chronic condition, necessitating ongoing surveillance and long-term management comparable to other chronic diseases, such as hypertension or diabetes [6–8]. Compared with other chronic condition guidelines, which offer clear, structured instructions on nutrition or physical activity, recommendations for long-term breast cancer survivors remain limited and poorly defined. Existing guidelines are generally broad and lack specificity regarding the particular breast cancer stage or survivorship they meant to address. This perspective challenges the notion that breast cancer is fully resolved after primary treatment, as both late treatment side effects and disease-related sequelae often persist and substantially influence survivors' long-term quality of life [9,10].

Breast cancer-related lymphedema (BCRL) is among the most common and distressing complications affecting approximately 30% of breast cancer survivors, usually within the first two years following treatment [11]. It results from damage or obstruction caused by surgery or radiation, leading to impaired lymphatic drainage, chronic inflammation, and persistent swelling [12]. Beyond physical symptoms such as swelling, heaviness, tightness, discomfort, pain, dermatological alterations, BCRL often cause functional limitations, body image disorders, and psychological distress, collectively contributing to reduced health-related quality of life (HRQoL) [9,10,13–18]. The severity and combination of these symptoms vary widely among individuals [19]. Although most of the studies focus on identifying upper limb symptoms and factors contributing to the development of BCRL, there remains a limited understanding of the complex interrelationships among lymphedema symptoms, knowledge crucial for improving patient care and quality of life [20–23].

Patient-reported outcome measures (PROMs) are increasingly used in clinical practice to assess HRQoL among lymphedema patients, where they capture patients' subjective experience and complement objective clinical indicators [22,24,25]. In BCRL, assessing HRQoL is particularly important due to the multidimensional impact across physical, psychological, and social domains. While generic QoL questionnaires used to evaluate BCRL patients' outcomes [26]. provide valuable insights about general aspects of survivorship, they often fail to capture the specific and multifaceted challenges associated with BCRL, such as functional limitations, body image concerns, and emotional distress. To address these limitations, disease-specific instruments have been developed to more accurately capture symptom burden and functional impact [27–30].

One of the most widely used tools regarding this manner is the Lymphedema Quality of Life Questionnaire (LYMQoL), designed to assess upper and lower limb

lymphedema [26,31,32]. Originally developed in English, it has been culturally adapted and validated in several countries, including Italy, Sweden, Turkey, the United Kingdom, Korea, China, and the Netherlands. Across these diverse populations, the instrument has demonstrated strong psychometric properties, supporting its utility for both clinical care and research [26,29,33–39]. LYMQoL enables a nuanced and multidimensional evaluation of patient-reported outcomes across Appearance, Function, Symptom, and Mood domains, thereby guiding personalised care and interventions aimed at improving HRQoL among women with BCRL [9,32,40]. However, findings suggest that LYMQoL scores do not always correlate with objective clinical measures such as limb volume, suggesting potential limitations in construct validity [29,41].

Despite the widespread international use of LYMQoL, no validated Croatian version of the instrument exists for women with BCRL. Considering that lymphedema assessment should encompass not only objective measurements but also self-reported experiences, the adaptation of a culturally appropriate, disease-specific tool is essential [11,13,14,18,42–44]. The availability of such an instrument would enable more accurate evaluation of patients' needs, enable monitoring of treatment outcomes, and ultimately support patient-centred care in Croatia.

Therefore, the primary aim of this study was to translate and validate the Croatian version of the LYMQoL for upper limb lymphedema, and to examine its psychometric properties with respect to validity, reliability, and factor structure in a population of Croatian breast cancer survivors with BCRL. The secondary aim was to explore the relationship between LYMQoL-UL-CRO (Lymphedema Quality of Life-Upper Limb-Croatian) scores and objective clinical indicators of lymphedema (upper limb volume difference) to assess the construct validity of the questionnaire and to better understand the association between self-reported quality of life and clinical measures.

2. Materials and Methods

2.1. Ethical Approval

The study protocol was approved by the Ethical Committee of the University Hospital Split (protocol code 2181-147/01/06/LJ.Z.-23-2) on 28 February 2023. This study was conducted in accordance with the principles of the Declaration of Helsinki. Before enrolment in the study, all participating women were informed about the nature of the study, and written informed consent was obtained.

2.2. Study Population

A total of 95 breast cancer survivors participated in this prospective observationalcross-sectional study conducted between 1 November 2023 to 30 March 2024. Participants were recruited from the Department of Physical Medicine, Rehabilitation, with Rheumatology at University Hospital Split, specifically among breast cancer survivors attending follow-up and treatment at the Lymphedema Daily Clinic. The eligibility criteria of the study population were: women aged 18 years or older who had completed treatment for unilateral breast cancer at least six months before study enrolment. The exclusion criteria were: women with bilateral mastectomy or metastatic breast cancer, cognitive impairments, pre-existing arm lymphedema before the initiation of breast cancer treatment, and active lymphedema treatment within three months before enrolment. Following the application of these exclusion criteria, data from 8 participants were excluded from the final analysis. Therefore, the final analysis was conducted on 87 breast cancer survivors (Figure 1).

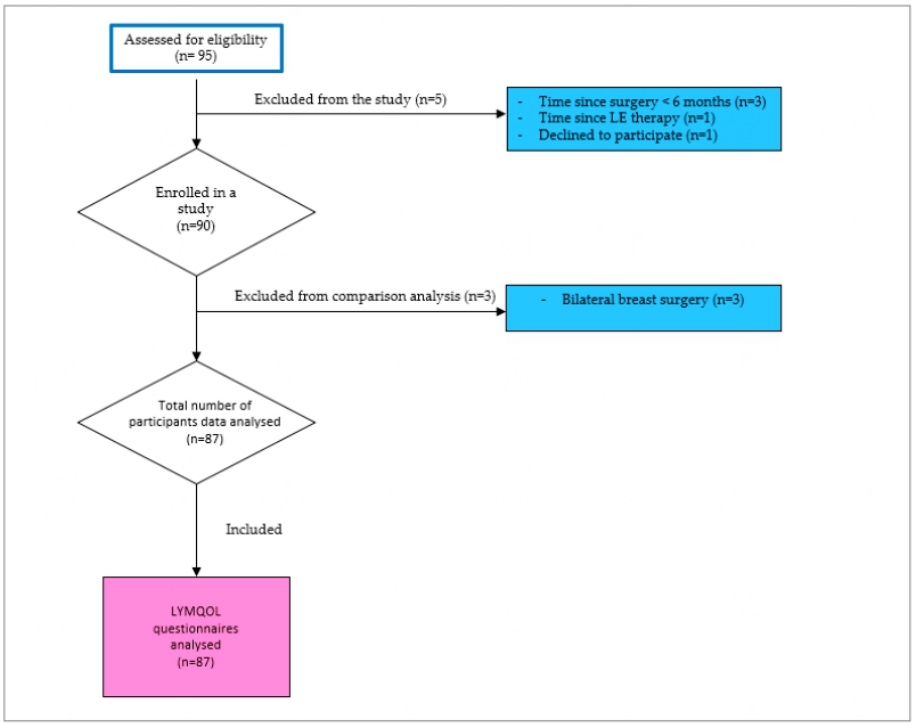

Figure 1. Flowchart of participants' enrolment. White boxes indicate stages of participant assessment and inclusion, blue boxes indicate reasons for exclusion, and the pink box indicates the final sample included in the LYMQOL questionnaire analysis.

2.3. Lymphedema Diagnosis

2.3.1. Volume Measurements of the Upper Limbs

The volume of the upper limbs was determined using a mathematical formula to calculate the relative difference in volume between the affected and the contralateral upper limb [44–46]. The standardised protocol used was described in detail in a previously published study [47].

In the present analysis, we adopted a lower threshold for relative volume change (RVC $\geq$ 5%) to enable the detection of early clinical lymphedema [13,48–52]. Although an RVC $\geq$ 10% is commonly used as the diagnostic criterion for clinically manifest BCRL, evidence suggests that smaller but measurable increases in arm volume may already reflect early pathophysiological changes [45,47–49,51]. To capture both stages, patients were classified into two groups: those with smaller volume differences (RVC < 5%), indicating subclinical BCRL, and those with larger volume differences (RVC $\geq$ 5%), indicating early clinical BCRL [46,53]. All of the participants (n = 87) completed the Lymphedema Quality of Life Questionnaire-Upper Limb-Croatian (LYMQoL-UL-CRO), Short-Form Health Survey with 36 Items (SF-36), and Pain Intensity Numerical Rating Scale (PINRS) questionnaires on the day of limb volume assessment.

2.3.2. Patients' Self-Perceived Lymphedema

As in previous research, self-perceived BCRL was classified based on participants' responses to a standardised question asked by the researcher, "At the moment, does your arm at the side of the surgery feel swollen?" A positive response was classified as the presence of BCRL, whereas a negative response was classified as its absence [54,55]. Women

who reported self-perceived BCRL were further investigated regarding the perceived arm swelling (mild, moderate, or severe) [54,55].

2.4. Instruments/Outcome Measures

2.4.1. Lymphedema Quality of Life Questionnaire-Arm (LYMQoL-Arm)

The LYMQoL—Arm questionnaire was developed by Keeley et al. in 2010 as a disease-specific instrument for assessing health-related quality of life (HRQoL) in patients with lymphedema [26]. It is a self-administered tool comprising 21 items. The first 20 items assess the impact of lymphedema on HRQOL across four domains: function, appearance, symptoms, and mood. Specifically, the function domain includes items 1–3, with item 1 further divided into eight sub-items (1a to 1h); the Appearance domain comprises items 4–8; the Symptoms domain covers items 9–14; and the Mood domain comprises items 15–20. Each item is rated on a four-grade Likert-like scale as Not at all (1); A little (2); Quite a bit (3) or A lot (4), with higher scores indicating lower HRQoL. Domain scores are calculated by summing the responses within each domain and dividing by the number of items answered. The four domain-specific summary scores are then analysed collectively. If more than 50% of the items in a domain were left unanswered, the corresponding domain score is assigned a value of zero. The final item (item 21) assesses global HRQoL, on an 11-point numerical rating scale ranging from 0 (poor HRQoL) to 10 (excellent HRQoL). For this study, we administered the translated and culturally adopted Croatian version of the LYMQoL questionnaire, Lymphedema Quality of Life Questionnaire-Upper Limb-Croatian (LYMQOL-UL-CRO) [26].

2.4.2. Short-Form Health Survey with 36 Items (SF-36)

Assessing criterion validity requires comparison with a recognised gold standard. In most studies, authors have relied on the SF-36 questionnaire [29,33]. The SF-36 is a self-reported measure of general health-related quality of life (HRQoL), an internationally recognised questionnaire, with a validated Croatian version available [54,56]. It comprises eight distinct scales. The Physical Component Summary (PCS) of HRQoL includes Physical Functioning (10 items), Bodily Pain (2 items), Role Limitations due to Physical Health (4 items), and General Health Perceptions (5 items). These domains collectively assess the physical aspects of HRQoL. The Mental Component Summary (MCS) includes Vitality (4 items), Social Functioning (2 items), Role Limitations due to Emotional Problems (3 items), and Mental Health (5 items), capturing the psychological and social dimensions of HRQoL [56]. For this study, we administered the Croatian version of the SF-36. Scoring was conducted following a standardised 3-step procedure, in accordance with the User's Manual of the Croatian version [56]. To derive the two higher-order summary scores: Physical Component Summary (PCS) and Mental Component Summary (MCS) [56,57]. The final score ranges between 0 and 100. In contrast to LYMQoL, the score is directly proportional to overall QoL, meaning a higher SF-36 score demonstrates higher HRQoL [36].

2.4.3. Pain Intensity Numerical Rating Scale (PINRS)

An 11-point Pain intensity numerical rating scale (PINRS) ranging from 0 (no pain) to 10 (worst possible pain) was used, asking participants to rate their current pain intensity [58]. The PINRS is a widely used, valid, and reliable instrument for quantifying subjective pain perception. It is simple to administer and easily understood by patients. Higher scores reflect greater pain intensity [58,59]. In this study, participants were asked to rate their current and worst levels of pain using the PINRS.

2.5. Translation and Cross-Cultural Adaptation Process

Following permission obtained from the copyright holder (Vaughan Keeley) [26], translation and cross-cultural adaptation of the LYMQoL-arm questionnaire into Croatian followed international guidelines [60].

2.5.1. Forward Translation

Forward translation from the original English version was undertaken independently by two Croatian lymphedema specialists (A.P. and I.K.K.). They were instructed to capture the conceptual meaning of the items while employing colloquial language to ensure comprehensibility for the average patient.

2.5.2. Reconciliation

Discrepancies between the two versions were critically reviewed, and a consensus was reached to produce a unified preliminary Croatian version.

2.5.3. Back Translation

This version was then subjected to backward translation into English by two bilingual professional translators (T.K. and I.D.), who were blinded to the original questionnaire.

2.5.4. Back Translation Review and Harmonisation

An expert committee of two professional translators and two local rehabilitation professionals fluent in English and experienced in the clinical and methodological aspects of lymphedema (physiatrists, A.P., and physiotherapist, I.K.K.), reviewed the semantic, idiomatic, and conceptual equivalence of the items and response options. Consensus was achieved on a pre-final version that aimed to preserve the meaning of the source text while expressing it in accessible lay language.

2.5.5. Cognitive Debriefing

The pre-final Croatian version was pilot tested in a group of ten women with arm lymphedema of varying ages and socioeconomic backgrounds, all treated at the University Hospital Split. After completing the questionnaire, participants underwent cognitive debriefing to assess the appropriateness, cultural relevance, and clarity of the questionnaire in detail.

2.5.6. Review of Cognitive Debriefing Results and Finalisation

Based on the feedback obtained, the expert committee finalised the text, resulting in the definitive Croatian version, LYMQoL-UL-CRO (available upon request from the authors upon request).

2.5.7. Proofreading and Editing

The final version was proofread by all forward translators. Authors have developed a visually clear layout suitable for printing, performed the final editing and formatting

2.6. Reliability

2.6.1. Internal Consistency

The psychometric validation of the LYMQoL-UL-CRO followed a rigorous methodological framework. Reliability was assessed through internal consistency with Cronbach's α for all domains (Function, Appearance, Symptoms, Mood).

2.6.2. Test–Retest Reliability

Participants were asked to complete LYMQoL-UL-CRO Arm twice with an interval of ten days. All participants completed the first questionnaire on the same day that limb volume measurements were taken. The retest was completed after ten days by 68 participants. The test–retest reliability was calculated using intraclass correlation coefficients derived from retest via a two-way random-effects model. Additionally, the reliability of the LYMQoL-UL-CRO was assessed by calculating the Standard Error of Measurement (SEM) and the Smallest Real Difference (SRD) for each domain.

2.7. Validation

2.7.1. Content Validity

Content validity was explored by administering a short follow-up questionnaire to the first 47 participants after completion of the LYMQoL-UL-CRO. Six questions assessed clarity, comprehensibility, and ease of use, as well as whether any items or response categories appeared redundant.

2.7.2. Criterion and Construct Validity

Construct validity was examined by assessing Spearman's rank correlations, assessing associations between LYMQoL-UL-CRO domains and SF-36 physical and mental component summaries (PCS and MCS) as gold standards, and Association with current and worst pain intensity as measured by Numerical rating scale (PINRS) was also assessed.

Criterion validity was examined by comparing LYMQoL-UL-CRO domain scores with established measures, including the SF-36 PCS and MCS and the Numerical Rating Scale (PINRS) for current and worst pain intensity, using Spearman's rank correlation coefficients to assess the strength and direction of associations.

2.7.3. Discriminant Validity

Discriminant validity was tested by comparing LYMQoL-UL-CRO scores between participants with clinical (RVC $\geq$ 5%) and those with subclinical (RVC < 5%) lymphedema groups using Welch's *t*-test.

2.8. Responsiveness

Participants were also asked whether the instrument adequately addressed the challenges they experienced due to BCRL, whether completion time was acceptable, and how long it took them to complete the questionnaire.

2.9. Factor Structure

The factor structure was examined using exploratory factor analysis (EFA) with Varimax rotation, retaining factors with eigenvalues greater than 1. The Kaiser-Meyer-Olkin (KMO) measure and Bartlett's test of sphericity confirmed data suitability.

2.10. Floor/Ceiling Effects

Floor/Ceiling Effects were also evaluated by calculating the proportions of participants scoring the minimum or maximum possible values in each domain, with thresholds set at <15%.

2.11. Quality of Evidence for the Measurement Properties of LYMQoL

The quality of evidence for the measurement properties of the LYMQoL questionnaire in this study was evaluated using the Consensus-based Standards for the selection of health Measurement Instruments (COSMIN) methodology. Each measurement property assessed in our dataset was rated according to the COSMIN criteria for good measurement

properties. Methodological quality was judged using the COSMIN Risk of Bias checklist, and ratings (sufficient, insufficient, or indeterminate) were assigned for each property based on the observed results [30,61].

2.12. Statistical Analysis

Statistical analysis was performed using IBM SPSS Statistics, Version 26 (IBM Corp., Armonh, NY, USA) software. Internal consistency was measured with Cronbach's alpha to assess the reliability of each domain. Test–retest reliability was determined by having participants complete the LYMQoL-UL-CRO on two occasions, calculating the intraclass correlation coefficient (ICC) using a two-way random effects model. Construct validity was assessed by calculating correlations. For data that were not normally distributed, we used Spearman's rank correlation coefficient, while for normally distributed data, we used Pearson's correlation coefficient. Factor structure was examined through exploratory or confirmatory factor analysis with Varimax rotation, and the suitability of the data was checked using the Kaiser-Meyer-Olkin (KMO) measure and Bartlett's test of sphericity. Floor and ceiling effects were assessed to ensure appropriate response distribution, with thresholds set at 15%. For group comparisons, non-parametric tests such as the Kruskal–Wallis analysis of variance, Mann–Whitney U-tests, and Welch's *t*-test were used. Missing data were handled by multiple imputations with five imputed datasets, and the significance level was set at $p < 0.05$.

3. Results

3.1. Translation Process

The translation process is described in detail in Section 2. Only minor differences were identified across four forward translations due to the favourably simple language used in the original version. A review of the backward translation showed near complete equivalence to the original English version. The formatted final version of LYMQoL-UL-CRO is available from the authors upon request.

3.2. Participants' Demographics and Treatment-Related Characteristics

Data from 87 breast cancer survivors were analysed, with an average interval of six years between completion of breast cancer treatment and study enrolment. Approximately 60% of participants had undergone mastectomy and total axillary lymph node dissection. In 54% of cases, surgery was performed on the dominant side of the body. Detailed data on participants' sociodemographic and treatment-related characteristics are summarised in Table 1.

Table 1. Characteristics of participants (n = 87).

Variable	Measure/Category	Value
Age (years)	M ± SD [1]	58.47 ± 8.95
BMI [2] (kg/m^2)	M ± SD	27.74 ± 5.64
Marital status n (%)	Married	54.84%
	Single	18.28%
	Widowed	15.05%
Education level n (%)	High school diploma	50.54%
	Bachelor's degree	21.51%
	Primary school	13.98%
Household income n (%)	<1000 €	38 (41.8%)
	1000–2000 €	31 (34.1%)
	>2000 €	16 (17.6%)
Years since the BC [3] surgery	M ± SD	6.25 ± 5.33

Table 1. *Cont.*

Variable	Measure/Category	Value
Type of the BC surgery; n (%)	Breast conserving	41.4%
	Mastectomy	58.6%
Lymph node removal; n (%)	SLND [4]	35 (40.2%)
	ALND [5]	52 (59.8%)
Radiotherapy; n (%)	Yes	75.9%
	No	24.1%
Chemotherapy; n (%)	Yes	60.9%
	No	39.0%

Note:[1] mean ± standard deviation; [2] Body Mass Index; [3] Breast Cancer; [4] Sentinel Lymph Node Biopsy; [5] Axillary Lymph Node Biopsy.

Data from 87 breast cancer survivors were analysed, with detailed results presented in Table 2. Participants were stratified into two subgroups based on relative volume change (RVC < 5% vs. RVC ≥ 5%). As shown in Table 2, individuals with RVC ≥ 5% were significantly older than those with RVC < 5% (60.5 ± 10.9 vs. 55.3 ± 9.8 years; $p = 0.021$) and more frequently reported swelling (85.1% vs. 53.8%; $p = 0.001$). No significant between-group differences were observed for body mass index, time since surgery, dominant arm involvement, mastectomy, axillary lymph node dissection, or adjuvant therapies (radiotherapy, chemotherapy, or endocrine therapy).

Table 2. Basic characteristics of participants by lymphedema subgroup: clinical lymphedema (RVC ≥ 5%) and subclinical lymphedema (RVC < 5%).

Variable	RVC [1] < 5% ($n = 40$)	RVC ≥ 5% ($n = 47$)	p-Value
Age (years); M ± SD	55.3 ± 9.8	60.5 ± 10.9	0.021 *
BMI [2] (kg/m^2); M ± SD	26.8 ± 4.9	28.7 ± 5.2	0.084
Time since surgery (years); M ± SD	6.2 ± 4.8	7.9 ± 5.4	0.137
Dominant arm affected; n (%)	13 (33.3%)	19 (40.4%)	0.505
Mastectomy; n (%)	16 (41.0%)	25 (53.2%)	0.247
ALND [3]; n (%)	19 (48.7%)	31 (66.0%)	0.096
Therapy; n (%)			
Radiotherapy; n (%)	30 (76.9%)	38 (80.9%)	0.648
Chemotherapy; n (%)	25 (64.1%)	34 (72.3%)	0.417
Endocrine therapy; n (%)	27 (69.2%)	35 (74.5%)	0.573
Self-reported swelling; n (%)	21 (53.8%)	40 (85.1%)	0.001 **

Note: [1] Relative Volume Change; [2] Body Mass Index; [3] Axillary Lymph Node Dissection, * $p < 0.05$; ** $p < 0.01$.

3.3. Reliability

3.3.1. Internal Consistency

All LYMQoL-UL-CRO domains showed adequate internal consistency ($\alpha > 0.70$). The Symptoms and Function domains demonstrated the highest reliability ($\alpha = 0.91$ and 0.85, respectively), followed by Appearance ($\alpha = 0.85$). Although the Mood domain initially showed lower internal consistency ($\alpha = 0.75$), its reliability markedly improved at retest ($\alpha = 0.92$), indicating temporal stability of this subscale, with detailed results presented in Table 3.

Table 3. Cronbach's alpha coefficients for the LYMQoL Arm.

LYMQoL [1] Domain	Cronbach's α	Cronbach's α Retest
Function	0.850	0.791
Appearance	0.846	0.855
Symptoms	0.907	0.901
Mood	0.748	0.921

Note:[1] Lymphedema Quality of Life Questionnaire.

3.3.2. Test–Retest Reliability

All domains show moderate reliability (ICC 0.68–0.73). The analysis shows adequate test–retest reliability, though slightly lower in the Appearance domain (Table 4).

Table 4. The reliability of the LYMQoL-UL-CRO was assessed through test–retest consistency.

LYQMoL Domain	Test (M ± SD) [1]	Retest (M ± SD)	ICC [2]	*p*-Value	SEM [3]	SRD [4]
Function	2.1 ± 0.7	2.0 ± 0.6	0.71	<0.01	0.38	1.05
Appearance	2.0 ± 0.8	1.9 ± 0.7	0.68	<0.01	0.45	1.25
Symptoms	2.2 ± 0.6	2.1 ± 0.5	0.73	<0.01	0.31	0.86
Mood	2.0 ± 0.7	1.9 ± 0.6	0.69	<0.01	0.39	1.08
Global	6.3 ± 2.1	6.1 ± 1.9	0.70	<0.01	1.15	3.19

Note: [1] mean ± standard deviation; [2] ICC—Intraclass Correlation Coefficient (two-way random effects model for absolute agreement); [3] Standard Error of Measurement = SD × $\sqrt{(1 - ICC)}$; [4] Smallest Real Difference = 1.96 × $\sqrt{2}$ × SEM.

The reliability of the LYMQoL-UL-CRO was assessed by calculating the Standard Error of Measurement (SEM) and the Smallest Real Difference (SRD) for each domain. SEM quantifies the expected variability in repeated measurements, ranging from 0.31 in the Symptoms domain to 0.45 in the Appearance domain. The SRD, indicating the minimal change required to confidently assert a true difference beyond measurement error, ranged from 0.86 in Symptoms to 1.25 in Appearance.

3.4. Validity

3.4.1. Criterion and Construct Validity

Table 5 shows that the LYMQoL-UL-CRO Function ($\rho = -0.65$, $p < 0.001$) and Symptoms ($\rho = -0.70$, $p < 0.001$) domains have strong negative correlations with the SF-36 Physical Component Summary (PCS), while the Mood domain ($\rho = -0.60$, $p < 0.001$) has a moderate negative correlation with the SF-36 Mental Component Summary (MCS). The Appearance domain shows weak, non-significant correlations with SF-36 components ($p > 0.05$). These results support the construct validity of the LYMQoL-Arm.

Table 5. Correlation between LYMQoL-UL-CRO domains and SF-36 and PINRS measurements.

LYQMoL [1] Domain	SF-36 [2] PSC [3]	SF-36 MSC [4]	PINRS [5] Current	PINRS Worst
Function	−0.65 *	−0.20	0.29 *	0.29 *
Appearance	−0.30	−0.15	0.22 *	0.25 *
Symptoms	−0.70 *	−0.25	0.37 **	0.41 **
Mood	−0.40	−0.60 *	0.15	0.17

Note: [1] Lymphedema Quality of Life Questionnaire; [2] Short Form (36) Health Survey; [3] Physical Component Summary; [4] Mental Component Summary; [5] Numerical Rating Scale; * $p < 0.05$; ** $p < 0.01$.

The Symptoms domain had the strongest and statistically significant positive correlations with all PINRS variables ($p < 0.01$), indicating that higher symptom burden is associated with worse self-reported outcomes. In contrast, the Mood factor did not

show significant correlations with any PINRS variable ($p > 0.05$), while the Function and Appearance factors demonstrated weaker or only partially significant associations (Table 5).

3.4.2. Discriminant Validity

Discriminant validity is demonstrated in Table 6, as it compares LYMQoL-UL-CRO and SF-36 scores between clinical and subclinical lymphedema groups to show whether the questionnaire can distinguish between patients with different levels of disease.

Table 6. Comparison of LYMQoL-UL-CRO Factors and SF-36 Scores by lymphedema subgroup: clinical lymphedema (RVC ≥ 5%) and subclinical lymphedema (RVC < 5%).

Domain	RVC [1] < 5% (n = 40)	RVC ≥ 5% (n = 47)	F-Statistic	p-Value
LYQMoL [2]-Arm Function	1.23 ± 0.45	1.89 ± 0.52	4.23	0.016 *
LYQMoL-Arm Appearance	1.57 ± 0.31	1.72 ± 0.41	1.12	0.331
LYQMoL-Arm Symptoms	1.95 ± 0.61	2.78 ± 0.67	5.67	0.004 *
LYQMoL-Arm Mood	1.82 ± 0.39	2.45 ± 0.58	3.45	0.035 *
SF-36 [3] PSC [4]	42.1 ± 8.2	38.5 ± 7.6	2.98	0.087
SF-36 MSC [5]	48.3 ± 9.1	44.7 ± 8.9	1.75	0.189

Note: [1] Relative Lymphedema Change; [2] Lymphedema Quality of Life Questionnaire; [3] Short Form (36) Health Survey; [4] Physical Component Summary; [5] Mental Component Summary; * $p < 0.05$.

Patients with higher RVC (≥5%) scores reported significantly worse outcomes in LYMQoL-UL-CRO Function (F = 4.23, $p = 0.016$), Symptoms (F = 5.67, $p = 0.004$), and Mood (F = 3.45, $p = 0.035$) compared to those with RVC < 5%. No significant differences were observed for Appearance or SF-36 summary components (PSC/MSC).

3.4.3. Content Validity

The 47 participants all agreed that the questionnaire was simple to complete and that the response format was clear. None of the respondents thought the questionnaire was too long or included unnecessary questions. All respondents confirmed that the questionnaire addressed the challenges they encounter because of their lymphedema.

Responsiveness

None of the participants thought the time needed to finish the questionnaire was too long. With a minimum of two minutes and a maximum of ten, the average completion time was approximately five minutes.

3.5. Factor Analysis

EFA identified four factors that together explained 60.49% of the total variance: Function (34.66%), Appearance (10.41%), Symptoms (9.13%), and Mood (6.29%) (Table 7). All factor loadings exceeded the 0.3 threshold. The suitability of the data for factor analysis was confirmed by a high Kaiser-Meyer-Olkin (KMO) value of 0.89 and a statistically significant Bartlett's test of sphericity ($\chi^2 = 2104.32$, $p < 0.001$).

Table 7. Factor Analysis of the LYMQoL-UL-CRO.

LYMQoL [1] Arm	Function	Appearance	Symptoms	Mood	Communality
LQ [2] 1a	0.36	−0.19	0.39	0.03	0.45
LQ1b	0.34	0.28	0.54	0.12	0.63
LQ1c	0.62	0.15	0.43	0.02	0.68
LQ1d	0.44	0.03	0.62	0.09	0.67
LQ1e	0.76	−0.02	0.22	0.09	0.60

Table 7. *Cont.*

LYMQoL [1] Arm	Function	Appearance	Symptoms	Mood	Communality
LQ1f	0.85	0.12	0.04	0.14	0.77
LQ1g	0.38	0.07	0.59	0.07	0.65
LQ1h	0.87	−0.01	0.06	0.11	0.76
LQ2	0.20	0.39	0.47	0.21	0.60
LQ3	0.23	0.40	0.49	0.27	0.63
LQ4	0.12	0.86	0.23	−0.07	0.82
LQ5	−0.01	0.85	0.15	0.11	0.81
LQ6	−0.04	0.85	0.06	0.06	0.73
LQ7	0.06	0.73	0.25	0.20	0.71
LQ8	0.04	0.47	0.13	0.17	0.42
LQ9	0.06	0.21	0.73	0.14	0.64
LQ10	0.05	0.21	0.82	0.12	0.78
LQ11	0.02	0.22	0.82	0.13	0.78
LQ12	−0.04	0.22	0.79	0.33	0.81
LQ13	0.07	0.50	0.55	0.33	0.76
LQ14	0.12	0.38	0.41	0.55	0.68
LQ15	0.11	0.16	0.21	0.77	0.73
LQ16	0.14	0.24	0.16	0.73	0.71
LQ17	0.15	0.10	0.15	0.86	0.79
LQ18	0.01	0.26	0.14	0.72	0.70
LQ19	−0.07	−0.09	0.16	0.88	0.82
LQ20	−0.04	−0.03	−0.02	0.30	0.29

Note: [1] Lymphedema Quality of Life Questionnaire; [2] Lymphedema Question.

3.6. Floor and Ceiling Effects

Floor effects represent the percentage of participants scoring the minimum value (1), while ceiling effects indicate those scoring the maximum value (4). All values remain below the recommended 15% threshold, demonstrating appropriate questionnaire design without significant response clustering (Table 8). The slightly elevated floor effect in the Function domain (18.2% test/15.9% retest) suggests a mild tendency toward minimal impairment reporting in physical function items, consistent with findings in chronic lymphedema populations. Retest values show improved distribution, indicating stable measurement properties.

Table 8. Floor and ceiling effects across LYMQoL-UL-CRO domains in both questionnaires.

LYQMoL [1] domain	Floor (%)	Ceiling (%)	Floor (%)	Ceiling (%)
	Test		Retest	
Function	18.2	9.1	15.9	6.8
Appearance	12.7	5.4	9.8	4.1
Symptoms	8.3	3.9	6.2	2.7
Mood	10.6	4.8	7.5	3.6

Note: [1] Lymphedema Quality of Life Questionnaire.

3.7. Quality of Evidence for the Measurement Properties of LYMQoL

The assessment of the psychometric properties of the LYMQoL-UL-CRO questionnaire demonstrated very good characteristics in most domains. All results of the psychometric evaluation of the LYMQoL-UL-CRO, including methodological quality according to COSMIN criteria and overall quality of evidence ratings, are systematically summarised and presented in Table 9.

Table 9. Psychometric properties of LYMQoL-UL-CRO according to Consensus-based Standards for the selection of health Measurement INstruments (COSMIN) checklist.

Measurement Property	COSMIN [1] Criteria/Requirement	LYMQoL-UL-CRO [2] Results	Quality Assessment
Content Validity	Item relevance, clarity, coverage of all aspects of the construct	All items are relevant and clear; the construct is thoroughly covered	Very good
Structural Validity	Factor analysis performed; KMO [3] > 0.7; significant Bartlett test	KMO [3] = 0.876; 4-factor model confirmed by EFA [4]	Very good
Internal Consistency	Cronbach's alpha $\geq$ 0.70 for all domains	Function α = 0.85, Appearance α = 0.85, Symptoms α = 0.91, Mood α = 0.75	Very good
Reliability (Test–Retest)	ICC [5] > 0.70 for all domains	Function ICC = 0.71, Appearance ICC = 0.68, Symptoms ICC = 0.73, Mood ICC = 0.69 (CI [6] 0.61–0.78, $p < 0.01$).	Good
Measurement Error	SEM [7] and SRD [8] reported	SEM (Function: 0.38, Appearance: 0.45, Symptoms: 0.31, Mood: 0.39, Global: 1.15); SRD (Function: 1.05, Appearance: 1.25, Symptoms: 0.86, Mood: 1.08, Global: 3.19)	Adequate
Criterion Validity	Strong correlations with gold standards (SF-36 [9] PCS [10], MCS [11], PINRS [12])	Function r = -0.65 ($p < 0.001$), Symptoms r = -0.70 ($p < 0.001$) with SF-36 PCS; Mood r = -0.60 ($p < 0.001$) with SF-36 MCS; correlations with PINRS ranged from 0.22 to 0.41 ($p < 0.05$) for all domains except Mood	Very good
Construct Validity	Correlations with related constructs	Confirmed by Spearman's rank correlations with SF-36 PCS, MCS, and PINRS	Very good
Discriminant Validity	Differentiation between clinical and subclinical lymphedema	Significant differences in Function (F = 4.23, $p = 0.016$), Symptoms (F = 5.67, $p = 0.004$), Mood (F = 3.45, $p = 0.035$) domains	Very good
Responsiveness	Usability, completion time, floor and ceiling effects	Mean completion time approx. 5 min; floor effects 6.2–18.2%; ceiling effects 2.7–9.1% across domains	Very good
Cross-Cultural Validity	Equivalence of forward/back translation and adaptation	Near-complete equivalence, with minor linguistic adjustments	Very good

COSMIN—[1] COnsensus-based Standards for the selection of health Measurement INstruments; [2] LYMQoL—Lymphedema Quality of Life Questionnaire; UL—Upper Limb; CRO—Croatian version; [3] KMO—Kaiser-Meyer-Olkin measure of sampling adequacy; [4] EFA—Exploratory Factor Analysis; [5] ICC—Intraclass Correlation Coefficient; [6] CI—Confidence Interval; [7] SEM—Standard Error of Measurement; [8] SRD—Smallest Real Difference; [9] SF-36—Short Form Health Survey—36 Items; [10] PCS—Physical Component Summary; [11] MCS—Mental Component Summary; [12] PINRS—Numeric Rating Scale; F—F-statistic; p—probability value.

4. Discussion

The primary aim of this study was to translate and validate the Croatian version of the LYMQoL-UL questionnaire. Our findings demonstrate that the LYMQoL-UL-CRO

possesses strong psychometric properties, is culturally appropriate, and captures the multidimensional impact of BCRL on HRQoL in Croatian breast cancer survivors. Furthermore, in addition to the psychometric analyses, the quality of the LYMQoL-UL-CRO measurement properties was evaluated according to COSMIN guidelines, providing a structured and internationally recognised framework for assessing PROM quality [61]. Using the COSMIN Risk of Bias checklist, the methodological quality of each measurement property was judged as adequate, and all properties were subsequently rated against COSMIN criteria for good measurement performance. The LYMQoL-UL-CRO demonstrated sufficient quality of evidence for content validity, structural validity, internal consistency, reliability, measurement error, and construct validity. The certainty of evidence was graded as very good. This comprehensive COSMIN-based evaluation further supports the robustness of the Croatian version of the LYMQoL-Arm and confirms that it meets recommended standards for use in both clinical practice and research

In the scope of our knowledge, this is the first study to assess the validity and reliability of a lymphedema-specific quality of life instrument within the Croatian healthcare context.

4.1. Content Validity and Cultural Adaptation

The evaluation of content validity in this study confirmed that the Croatian version preserved the conceptual integrity of the original instrument. All participants found that the LYMQoL-UL-CRO was clear, comprehensive, and easy to complete, consistent with previous findings demonstrating LYMQoL items reflect concepts relevant to women with BCRL [26,62]. No missing items or conceptual inconsistencies were identified. These findings suggest that the translation accurately reflects the linguistic and cultural context of Croatian patients. This feedback process ensured conceptual item selection across multiple domains [62]. The overall consistency of findings with previous international adaptations confirms that LYMQoL-UL-CRO remains both a conceptual and practical equivalent to the original tool [26,29,41].

4.2. Reliability

The physiometric properties of the Croatian version of the LYMQoL-UL-CRO closely mirror findings from previous international studies, confirming its reliability and clinical relevance [29,33,38,41,63]. High internal consistency ($\alpha > 0.75$–0.91) and moderate test–retest reliability (ICC 0.68–0.73), individual consistent measurement across time, with slightly lower stability observed in the Appearance domain. Slightly reduced ICC values in this domain may be explained by day-to-day fluctuations in limb volume, particularly in milder cases [13,21,29,55]. Additionally, appearance perceptions can vary with transient swelling, mood fluctuations, or changes in body image, which naturally introduce greater variability. The chosen 10-day retest interval reflects a methodological trade-off: it is sufficiently long to minimise recall bias, yet long enough for natural symptom fluctuation to occur. Previous studies used shorter retest intervals (2–7 days), which likely reduced symptom variability and may therefore explain their comparatively higher ICC values [29,33].

Sensitivity testing further supported the instrument's precision and suitability for detecting true changes in individual symptoms and appearance over time. Low SEM and SRD values across all domains indicate that this tool provides consistent and dependent scores upon repeated measures [64]. These results demonstrate satisfactory measurement precision and stable psychometric properties, supporting its use in clinical monitoring and follow-up.

The slightly elevated floor effect in the Function domain suggests a mild tendency toward minimal impairment reporting in physical function items, consistent with findings in chronic lymphedema populations [15,21]. However, the reduction in the floor effect at

retest suggests improved distribution and supports the stability of measurement properties over time.

4.3. Validity

Construct and validity analysis revealed strong and theoretically consistent correlations between LYMQoL-UL-CRO and the SF-36 summary components. As expected, the Function and Symptoms domains correlated strongly and negatively with the SF-36 Physical Component Summary (PCS), while the Mood domain showed a moderate negative correlation with the Mental Component Summaries (MCS). These negative correlations are conceptually expected. Higher symptom burden or functional impairment on LYMQoL-UL-CRO necessarily reflects poorer perceived health status, resulting in lower SF-36 scores [28,65]. These relationships support the conceptual overlap between two measures and confirm that LYMQoL-UL-Cro appropriately captures both physical and psychological dimensions of HRQoL in BCRL and align with results from other cultural validations, where stronger associations with physical domains have been reported [29,33,36,37,41]. Moreover, similar results were obtained when comparing LYMQoL with other generic HRQoL instruments, such as the EQ-5D, EORTC QLQ-C30, and Nottingham Health Profile, which reinforce its construct validity and applicability across diverse populations [33,38,63].

Discriminant validity was also established as LYMQoL-UL-CRO successfully distinguished between participants with subclinical and early-clinically lymphedema (RVC $< 5\%$ vs. RVC $\geq 5\%$). Notably, this threshold is lower than the traditional criterion of $\geq 10\%$ volume increase typically used to define clinically evident lymphedema [45,46,51]. Yet LYMQoL-UL-CRO was still able to detect meaningful differences in HRQoL. These findings highlight the instrument's ability to capture HRQoL impairments even in relatively small but clinically important volume increases, underscoring its sensitivity in early disease stages [47,53,66].

Patients with greater RVC reported significantly worse Function, Symptoms, and Mood scores, confirming that the presence of clinically defined lymphedema meaningfully affects HRQoL. These results are consistent with previous studies showing that patients with more severe conditions experience increased arm heaviness, tightness, pain, and body image disturbance [18,28,36,67,68]. In contrast, neither perceived physical appearance nor overall health status, as assessed by the generic SF-36 questionnaire, differed significantly between groups. This finding suggests that disease-specific tools such as LYMQoL-UL-CRO are more sensitive to the subtle yet clinically meaningful impact of lymphedema on daily functioning and emotional adjustment, compared to generic instruments [28,33,63,65].

Given that LYMQoL-UL-CRO will primarily be used by rehabilitation team, its clinical utility extends beyond outcome evaluation to practical guidance for goal setting and treatment planning. The ability of this instrument to identify patients at risk of functional or emotional burden provides valuable support for clinicians' decision-making and helps determine when intensified monitoring or intervention may be warranted [69]. By enabling a detailed understanding of symptom burden and functional limitations, this instrument contributes to the development of an individualised, patient-centred model of lymphedema management [27,28,40]. Worsening of Function or Symptom scores can guide clinicians towards initiation or intensification of Complete Decongestive Therapy, adjusting compression therapy, exercise programmes, or referring patients for psychological support when emotional or appearance concerns arise [2].

Finally, its incorporation in routine follow-up care may also inform future updates of survivorship guidelines, particularly for breast cancer survivors, a population for whom current recommendations beyond five years post-treatment remain limited [2,6,70]. Its structured use within prospective surveillance models, administered preoperatively, early

postoperatively, and at regular follow-up intervals, enabling timely identification of meaningful changes that may precede detectable limb swelling [9]. While discriminant validity demonstrates an instrument's ability to differentiate between levels of clinically defined lymphedema, further interpretation is needed to understand how these clinical indicators relate to patients' subjective experiences.

4.4. Clinical Interpretation and Construct Relationships

Our results also contribute to the ongoing discussion regarding the relationship between clinical indicators and self-reported outcomes. Consistent with previous studies, HRQoL did not always correlate with objective measures such as limb volume, indicating that volume alone does not determine well-being [26,41]. Although increases in limb volume (RVC $\geq$ 5%) may signal lymphatic impairment [47,71,72], subjective experiences of symptoms and appearance often better reflect the true impact of lymphedema on QoL [22,26,41,55,71,73,74]. Recent studies further confirm this discrepancy, showing that limb volume only partially explains QoL variance, while subjective symptom burden is more strongly associated with functional limitations and emotional distress [75]. Our findings support this interpretation, as overall HRQoL did not differ significantly between women with higher and lower RVC values, suggesting that psychological and functional factors may play a greater role than physical swelling alone [22,26,41,55,76,77]. These results underscore the importance of individualised, patient-centred management strategies that integrate both subjective and objective assessments, as previously recommended [22,76,78]. Such an approach provides a more comprehensive understanding of patients' needs and may enhance the precision of therapeutic decision-making.

Interpretation of our findings should also consider current shifts in breast cancer surgery. Modern axillary management has reduced BCRL incidence compared to historical cohorts [8,13].

In our study, however, around 60% of women underwent ALND, and most of them received radiotherapy, indicating that the present results are more applicable to survivors at higher baseline risk.

Despite these shifts, LYMQoL-UL-CRO remains highly relevant in modern treatment pathways where subtle early volume changes, particularly following SLND and radiotherapy, still require careful monitoring. By enabling early detection of patient-reported impairments, the instrument supports a proactive and longitudinal approach to survivorship care [2].

4.5. Strengths and Limitations

The major strength of this study is its novelty; it represents the first validation of disease-specific PROM for upper limb lymphedema in Croatia. The study fills both a clinical and scientific gap by providing a culturally relevant tool with proven psychometric quality. The study achieved excellent feasibility and acceptability, demonstrated by a 100% completion rate, no missing responses, and a very short average completion time consistent with previous studies. Another strength lies in the comprehensive evaluation of both reliability and validity, as well as the instruments' proven ability to distinguish patients with different levels of disease severity, confirming their clinical utility and cross-cultural comparability. In contrast to the majority of prior research, our study incorporated an objective assessment of limb volume alongside subjective outcomes. Nevertheless, several limitations should be acknowledged. First, the cross-sectional design limits the ability to detect changes over time and prevents any causal interpretation between lymphedema severity and quality-of-life outcomes. Additionally, the retrospective and single-centr nature of the study may have introduced selection bias and further restricted causal inference.

The effective sample size was relatively small due to the 4:1 particle-to-participant ratio; a larger ratio would have improved the precision of the analyses. Moreover, because our institution is both a tertiary referral center and is the only regional facility providing specialised lymphedema care, the potential for spectrum bias exists, although comprehensive referral patterns may partially mitigate this. The LYMQoL instrument is also region-specific, designed primarily for upper-limb lymphedema, and therefore does not capture quality-of-life issues related to lymphedema at other anatomical sites. Future research should include larger, more diverse patient populations and employ longitudinal designs to assess sensitivity to change and responsiveness to interventions over time.

5. Conclusions

The Croatian LYMQoL-Arm questionnaire demonstrated strong psychometric properties, including high reliability, robust construct, and discriminant validity, and a clear factor structure. These findings confirm that the Croatian version is a reliable, sensitive, and culturally appropriate tool for assessing HRQoL in women with breast cancer-related lymphedema. Its implementation in clinical and research practice can enhance individualised patient assessment, enable early detection of disease impact, and contribute to improved survivorship care and long-term outcomes.

Importantly, our findings reinforce that volume measurements alone are insufficient to capture the full extent of patient burden. Objective changes should always be interpreted in conjunction with LYMQoL-UL-CRO scores to obtain a more accurate understanding of patients' lived experiences. Furthermore, symptom clusters such as pain, heaviness, tightness, and functional restriction may provide more clinically meaningful guidance for tailoring physiotherapy interventions than absolute differences in limb volume. By integrating both objective and patient-reported measures, clinicians can deliver more precise, responsive, and patient-centred lymphedema management.

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Informed Consent Statement: Before enrolment in the study, all participating women were informed about the nature of the study, and written informed consent was obtained.

Data Availability Statement: The data presented in this study are available on request from the corresponding author.

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Abbreviations

The following abbreviations are used in this manuscript:

TLA	Three-letter acronyms
LYMQoL	Lymphedema Quality of Life Questionnaire
SF-36	Short-Form Health Survey
PI-PINRS-11	Pain Intensity Numerical Rating Scale
RVC	Relative Volume Change
BCRL	Breast Cancer-Related Lymphedema
BMI	Body Mass Index
QoL	Quality of Life
HRQoL	Health-Related Quality of Life
UL	Upper Limb
CRO	Croatian
PROM	Patient Reported Outcome Measure
SF-36	Short Form Health Survey—36 Items
PCS	Physical Component Summary
MCS	Mental Component Summary
ICC	Intraclass Correlation Coefficient
CI	Confidence Interval;
KMO	Kaiser-Meyer-Olkin measure of sampling adequacy;
LQ	LYMQoL Question
SD	Standard Error of Measurement
α	Cronbach Alpha
EORTC QLQ C30	European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30.
EQ 5D	EuroQol 5-Dimensions questionnaire
PINRS	Numerical rating Scale
F	F-statistics
p	Probability value
SRD	Smallest Real Difference

References

1. Hazard-Jenkins, H.W. Breast Cancer Survivorship-Mitigating Treatment Effects on Quality of Life and Improving Survival. *Obstet. Gynecol. Clin. N. Am.* **2022**, *49*, 209–218. [CrossRef]
2. Pimentel-Parra, G.A.; García-Vivar, C.; Escalada-Hernández, P.; San Martín-Rodríguez, L.; Soto-Ruiz, N. Systematic review of clinical practice guidelines for long-term breast cancer survivorship: Assessment of quality and evidence-based recommendations. *Br. J. Cancer* **2025**, *133*, 178–193. [CrossRef] [PubMed]
3. Khajoei, R.; Ilkhani, M.; Azadeh, P.; Zohari Anboohi, S.; Heshmati Nabavi, F. Breast cancer survivors-supportive care needs: Systematic review. *BMJ Support. Palliat. Care* **2023**, *13*, 143–153. [CrossRef] [PubMed]
4. Brauer, E.R.; Ganz, P.A. Moving the Translational Needle in Breast Cancer Survivorship: Connecting Intervention Research to Clinical Practice. *J. Clin. Oncol.* **2022**, *40*, 2069–2073. [CrossRef]
5. Grilli, R.; Magrini, N.; Penna, A.; Mura, G.; Liberati, A. Practice guidelines developed by specialty societies: The need for a critical appraisal. *Lancet* **2000**, *355*, 103–106. [CrossRef] [PubMed]
6. Ayala de la Peña, F.; Antolín Novoa, S.; Gavilá Gregori, J.; González Cortijo, L.; Henao Carrasco, F.; Martínez Martínez, M.T.; Morales Estévez, C.; Stradella, A.; Vidal Losada, M.J.; Ciruelos, E. SEOM-GEICAM-SOLTI clinical guidelines for early-stage breast cancer (2022). *Clin. Transl. Oncol.* **2023**, *25*, 2647–2664. [CrossRef]

7. Biganzoli, L.C.M.; Conte, B.; Cortesi, L.; Criscitiello, C.D.M.L.; Fiorentino, A.; Levaggi, A.; Montemurro, F.; Marchio, C.; Tinterri, C.; Zambelli, A. *Breast Neoplasms Guidelines*; Associazione Italiana di Oncologia Medica: Milano, Italy, 2018.
8. Stangl, S.; Follmann, M.; Wenzel, G.; Langer, T.; Wöckel, A. Evidence-based guideline for the early detection, diagnosis, treatment and follow-up of breast cancer. In *Germany: German Guideline Program in Oncology (GGPO)*; The Association of the Scientific Medical Societies in Germany: Frankfurt, Germany, 2021; Volume 462.
9. Davies, C.; Levenhagen, K.; Ryans, K.; Perdomo, M.; Gilchrist, L. Interventions for Breast Cancer-Related Lymphedema: Clinical Practice Guideline from the Academy of Oncologic Physical Therapy of APTA. *Phys. Ther.* **2020**, *100*, 1163–1179. [CrossRef]
10. Jørgensen, M.G.; Toyserkani, N.M.; Hansen, F.G.; Bygum, A.; Sørensen, J.A. The impact of lymphedema on health-related quality of life up to 10 years after breast cancer treatment. *npj Breast Cancer* **2021**, *7*, 70. [CrossRef]
11. DiSipio, T.; Rye, S.; Newman, B.; Hayes, S. Incidence of unilateral arm lymphoedema after breast cancer: A systematic review and meta-analysis. *Lancet Oncol.* **2013**, *14*, 500–515. [CrossRef]
12. Földi, M. On the pathophysiology of arm lymphedema after treatment for breast cancer. *Lymphology* **1995**, *28*, 151–158.
13. McLaughlin, S.A.; Brunelle, C.L.; Taghian, A. Breast Cancer-Related Lymphedema: Risk Factors, Screening, Management, and the Impact of Locoregional Treatment. *J. Clin. Oncol.* **2020**, *38*, 2341–2350. [CrossRef] [PubMed]
14. Jørgensen, L.; Garne, J.P.; Søgaard, M.; Laursen, B.S. The experience of distress in relation to surgical treatment and care for breast cancer: An interview study. *Eur. J. Oncol. Nurs.* **2015**, *19*, 612–618. [CrossRef] [PubMed]
15. Pappalardo, M.; Starnoni, M.; Franceschini, G.; Baccarani, A.; De Santis, G. Breast Cancer-Related Lymphedema: Recent Updates on Diagnosis, Severity and Available Treatments. *J. Pers. Med.* **2021**, *11*, 402. [CrossRef] [PubMed]
16. Ridner, S.H.; Dietrich, M.S. Development and validation of the Lymphedema Symptom and Intensity Survey-Arm. *Support. Care Cancer* **2015**, *23*, 3103–3112. [CrossRef]
17. Eaton, L.H.; Narkthong, N.; Hulett, J.M. Psychosocial Issues Associated with Breast Cancer-Related Lymphedema: A Literature Review. *Curr. Breast Cancer Rep.* **2020**, *12*, 216–224. [CrossRef]
18. Anbari, A.B.; Wanchai, A.; Armer, J.M. Breast cancer-related lymphedema and quality of life: A qualitative analysis over years of survivorship. *Chronic Illn.* **2021**, *17*, 257–268. [CrossRef]
19. Shen, A.; Lukkahatai, N.; Zhang, Z.; Zhao, H.; Salim, N.A.; Han, G.; Qiang, W.; Lu, Q. Upper limb symptoms in breast cancer survivors with lymphedema: A latent class analysis and network analysis. *Asia Pac. J. Oncol. Nurs.* **2025**, *12*, 100713. [CrossRef]
20. Liu, Y.F.; Liu, J.E.; Zhu, Y.; Mak, Y.W.; Qiu, H.; Liu, L.H.; Yang, S.S.; Chen, S.H. Development and validation of a nomogram to predict the risk of breast cancer-related lymphedema Among Chinese breast cancer survivors. *Support. Care Cancer* **2021**, *29*, 5435–5445. [CrossRef]
21. Togawa, K.; Ma, H.; Smith, A.W.; Neuhouser, M.L.; George, S.M.; Baumgartner, K.B.; McTiernan, A.; Baumgartner, R.; Ballard, R.M.; Bernstein, L. Self-reported symptoms of arm lymphedema and health-related quality of life among female breast cancer survivors. *Sci. Rep.* **2021**, *11*, 10701. [CrossRef]
22. Hormes, J.M.; Bryan, C.; Lytle, L.A.; Gross, C.R.; Ahmed, R.L.; Troxel, A.B.; Schmitz, K.H. Impact of lymphedema and arm symptoms on quality of life in breast cancer survivors. *Lymphology* **2010**, *43*, 1–13.
23. Hayes, S.C.; Dunn, M.; Plinsinga, M.L.; Reul-Hirche, H.; Ren, Y.; Laakso, E.L.; Troester, M.A. Do Patient-Reported Upper-Body Symptoms Predict Breast Cancer-Related Lymphoedema: Results from a Population-Based, Longitudinal Breast Cancer Cohort Study. *Cancers* **2022**, *14*, 5998. [CrossRef]
24. Coriddi, M.; Dayan, J.; Sobti, N.; Nash, D.; Goldberg, J.; Klassen, A.; Pusic, A.; Mehrara, B. Systematic Review of Patient-Reported Outcomes following Surgical Treatment of Lymphedema. *Cancers* **2020**, *12*, 565. [CrossRef]
25. Chima, C.; Murray, B.; Moore, Z.; Costello, M.; George, S. Health-related quality of life and assessment in patients with lower limb lymphoedema: A systematic review. *J. Wound Care* **2022**, *31*, 690–699. [CrossRef] [PubMed]
26. Keeley, V.; Crooks, S.; Locke, J.; Veigas, D.; Riches, K.; Hilliam, R. A quality of life measure for limb lymphoedema (LYMQOL). *J. Lymphoedema* **2010**, *5*, 26–37.
27. Alfano, C.M.; Leach, C.R.; Smith, T.G.; Miller, K.D.; Alcaraz, K.I.; Cannady, R.S.; Wender, R.C.; Brawley, O.W. Equitably improving outcomes for cancer survivors and supporting caregivers: A blueprint for care delivery, research, education, and policy. *CA Cancer J. Clin.* **2019**, *69*, 35–49. [CrossRef]
28. Fu, M.R.; Axelrod, D.; Cleland, C.M.; Qiu, Z.; Guth, A.A.; Kleinman, R.; Scagliola, J.; Haber, J. Symptom report in detecting breast cancer-related lymphedema. *Breast Cancer Targets Ther.* **2015**, *7*, 345–352. [CrossRef]
29. Monticone, M.; Ferriero, G.; Keeley, V.; Brunati, R.; Liquori, V.; Maggioni, S.; Restelli, M.; Giordano, A.; Franchignoni, F. Lymphedema quality of life questionnaire (LYMQOL): Cross-cultural adaptation and validation in Italian women with upper limb lymphedema after breast cancer. *Disabil. Rehabil.* **2022**, *44*, 4075–4080. [CrossRef]
30. Meilani, E.; Zanudin, A.; Mohd Nordin, N.A. Psychometric Properties of Quality of Life Questionnaires for Patients with Breast Cancer-Related Lymphedema: A Systematic Review. *Int. J. Environ. Res. Public Health* **2022**, *19*, 2519.

31. Levenhagen, K.; Davies, C.; Perdomo, M.; Ryans, K.; Gilchrist, L. Diagnosis of Upper Quadrant Lymphedema Secondary to Cancer: Clinical Practice Guideline From the Oncology Section of the American Physical Therapy Association. *Phys. Ther.* **2017**, *97*, 729–745. [CrossRef]
32. Grünherz, L.; Hulla, H.; Uyulmaz, S.; Giovanoli, P.; Lindenblatt, N. Patient-reported outcomes following lymph reconstructive surgery in lower limb lymphedema: A systematic review of literature. *J. Vasc. Surg. Venous Lymphat. Disord.* **2021**, *9*, 811–819.e812. [CrossRef]
33. Borman, P.; Yaman, A.; Denizli, M.; Karahan, S.; Özdemir, O. The reliability and validity of Lymphedema Quality of Life Questionnaire-Arm in Turkish patients with upper limb lymphedema related with breast cancer. *Turk. J. Phys. Med. Rehabil.* **2018**, *64*, 205–212. [CrossRef]
34. Uhm, K.E.; Yeo, S.M.; Yoo, J.S.; Hwang, J.H. Reliability and Validity of the Korean Version of the Lymphedema Quality of Life Questionnaire in Breast Cancer-Related Lymphedema Patients. *Lymphat. Res. Biol.* **2023**, *21*, 187–193. [CrossRef] [PubMed]
35. Zhou, Y.; Xiu, B.; Zhang, Q.; Wu, J. Cross-cultural adaptation and psychometric validation of lymphedema patient-reported outcome measurements in Chinese breast cancer patients [abstract]. *Cancer Res.* **2024**, *84*, PO3-11. [CrossRef]
36. Schulz, T.; Warg, M.L.; Heister, S.; Lidzba, K.; Ciklatekerlio, G.; Molter, Y.; Langer, S.; Nuwayhid, R. Translation, Cross-Cultural Adaptation and Validation of the Lymphedema Quality of Life Questionnaire (LYMQOL) in German-Speaking Patients with Upper Limb Lymphedema. *Healthcare* **2024**, *12*, 1881. [CrossRef]
37. van de Pas, C.B.; Biemans, A.A.; Boonen, R.S.; Viehoff, P.B.; Neumann, H.A. Validation of the Lymphoedema Quality-of-Life Questionnaire (LYMQOL) in Dutch Patients Diagnosed with Lymphoedema of the Lower Limbs. *Phlebology* **2016**, *31*, 257–263. [CrossRef]
38. Liang, Z.Y.; Long, X.; Yang, E.L.; Li, Y.Z.; Li, Z.J.; Xu, M.; Zhang, B.F.; Yu, N.Z.; Huang, J.Z. Reliability and Validity of the Chinese Version of the Lymphedema Quality of Life Questionnaire. *Chin. Med. Sci. J.* **2021**, *36*, 295–306. [CrossRef]
39. Taylor, R.; Jayasinghe, U.W.; Koelmeyer, L.; Ung, O.; Boyages, J. Reliability and validity of arm volume measurements for assessment of lymphedema. *Phys. Ther.* **2006**, *86*, 205–214. [CrossRef]
40. Ryans, K.; Perdomo, M.; Davies, C.C.; Levenhagen, K.; Gilchrist, L. Rehabilitation interventions for the management of breast cancer-related lymphedema: Developing a patient-centered, evidence-based plan of care throughout survivorship. *J. Cancer Surviv.* **2023**, *17*, 237–245. [CrossRef] [PubMed]
41. Wedin, M.; Fredrikson, M.; Ahlner, E.; Falk, A.; Sandström, Å.; Lindahl, G.; Rosenberg, P.; Kjølhede, P. Validation of the Lymphoedema Quality of Life Questionnaire (LYMQOL) in Swedish cancer patients. *Acta Oncol.* **2020**, *59*, 365–371. [CrossRef]
42. Rockson, S.G. Lymphedema after Breast Cancer Treatment. *N. Engl. J. Med.* **2018**, *379*, 1937–1944. [CrossRef] [PubMed]
43. Armer, J.M.; Stewart, B.R. A comparison of four diagnostic criteria for lymphedema in a post-breast cancer population. *Lymphat. Res. Biol.* **2005**, *3*, 208–217. [CrossRef]
44. Ridner, S.H.; Montgomery, L.D.; Hepworth, J.T.; Stewart, B.R.; Armer, J.M. Comparison of upper limb volume measurement techniques and arm symptoms between healthy volunteers and individuals with known lymphedema. *Lymphology* **2007**, *40*, 35–46.
45. Deltombe, T.; Jamart, J.; Recloux, S.; Legrand, C.; Vandenbroeck, N.; Theys, S.; Hanson, P. Reliability and limits of agreement of circumferential, water displacement, and optoelectronic volumetry in the measurement of upper limb lymphedema. *Lymphology* **2007**, *40*, 26–34. [PubMed]
46. Hayes, S.; Cornish, B.; Newman, B. Comparison of methods to diagnose lymphoedema among breast cancer survivors: 6-month follow-up. *Breast Cancer Res. Treat.* **2005**, *89*, 221–226. [CrossRef]
47. Klarić-Kukuz, I.; Mršić, D.B.; Matana, A.; Barun, B.; Aljinović, J.; Marinović-Guić, M.; Poljičanin, A. High-Frequency Ultrasonography Imaging: Anatomical Measuring Site as Potential Clinical Marker for Early Identification of Breast Cancer-Related Lymphedema. *Biomedicines* **2025**, *13*, 1396. [CrossRef]
48. Ancukiewicz, M.; Russell, T.A.; Otoole, J.; Specht, M.; Singer, M.; Kelada, A.; Murphy, C.D.; Pogachar, J.; Gioioso, V.; Patel, M.; et al. Standardized method for quantification of developing lymphedema in patients treated for breast cancer. *Int. J. Radiat. Oncol. Biol. Phys.* **2011**, *79*, 1436–1443. [CrossRef]
49. Soran, A.; Ozmen, T.; McGuire, K.P.; Diego, E.J.; McAuliffe, P.F.; Bonaventura, M.; Ahrendt, G.M.; DeGore, L.; Johnson, R. The importance of detection of subclinical lymphedema for the prevention of breast cancer-related clinical lymphedema after axillary lymph node dissection; a prospective observational study. *Lymphat. Res. Biol.* **2014**, *12*, 289–294. [CrossRef] [PubMed]
50. Yen, T.W.; Fan, X.; Sparapani, R.; Laud, P.W.; Walker, A.P.; Nattinger, A.B. A contemporary, population-based study of lymphedema risk factors in older women with breast cancer. *Ann. Surg. Oncol.* **2009**, *16*, 979–988. [CrossRef]
51. Stout Gergich, N.L.; Pfalzer, L.A.; McGarvey, C.; Springer, B.; Gerber, L.H.; Soballe, P. Preoperative assessment enables the early diagnosis and successful treatment of lymphedema. *Cancer* **2008**, *112*, 2809–2819. [CrossRef] [PubMed]
52. Specht, M.C.; Miller, C.L.; Russell, T.A.; Horick, N.; Skolny, M.N.; O'Toole, J.A.; Jammallo, L.S.; Niemierko, A.; Sadek, B.T.; Shenouda, M.N.; et al. Defining a threshold for intervention in breast cancer-related lymphedema: What level of arm volume increase predicts progression? *Breast Cancer Res. Treat.* **2013**, *140*, 485–494. [CrossRef]

53. Czerniec, S.A.; Ward, L.C.; Refshauge, K.M.; Beith, J.; Lee, M.J.; York, S.; Kilbreath, S.L. Assessment of breast cancer-related arm lymphedema--comparison of physical measurement methods and self-report. *Cancer Investig.* **2010**, *28*, 54–62. [CrossRef] [PubMed]
54. Boyages, J.; Vicini, F.A.; Shah, C.; Koelmeyer, L.A.; Nelms, J.A.; Ridner, S.H. The Risk of Subclinical Breast Cancer-Related Lymphedema by the Extent of Axillary Surgery and Regional Node Irradiation: A Randomized Controlled Trial. *Int. J. Radiat. Oncol. Biol. Phys.* **2021**, *109*, 987–997. [CrossRef]
55. Brunelle, C.L.; Roberts, S.A.; Horick, N.K.; Gillespie, T.C.; Jacobs, J.M.; Daniell, K.M.; Naoum, G.E.; Taghian, A.G. Integrating Symptoms Into the Diagnostic Criteria for Breast Cancer-Related Lymphedema: Applying Results From a Prospective Surveillance Program. *Phys. Ther.* **2020**, *100*, 2186–2197. [CrossRef]
56. Juresa, V.; Ivanković, D.; Vuletić, G.; Babić-Banaszak, A.; Srcek, I.; Mastilica, M.; Budak, A. The Croatian Health Survey--SF-36: I. General quality of life assessment. *Coll. Antropol.* **2000**, *24*, 69–78.
57. Maslić Sersić, D.; Vuletić, G. Psychometric evaluation and establishing norms of Croatian SF-36 health survey: Framework for subjective health research. *Croat. Med. J.* **2006**, *47*, 95–102.
58. Farrar, J.T.; Young, J.P., Jr.; LaMoreaux, L.; Werth, J.L.; Poole, M.R. Clinical importance of changes in chronic pain intensity measured on an 11-point numerical pain rating scale. *Pain* **2001**, *94*, 149–158. [CrossRef] [PubMed]
59. Schuster, S.; Lončarić Kelečić, I.; Bilić, M.; Begić, M.; Pate, J.W. Conceptualization of pain in Croatian adults: A cross-sectional and psychometric study. *Croat. Med. J.* **2024**, *65*, 473–482. [CrossRef]
60. Cruchinho, P.; López-Franco, M.D.; Capelas, M.L.; Almeida, S.; Bennett, P.M.; Miranda da Silva, M.; Teixeira, G.; Nunes, E.; Lucas, P.; Gaspar, F. Translation, Cross-Cultural Adaptation, and Validation of Measurement Instruments: A Practical Guideline for Novice Researchers. *J. Multidiscip. Healthc.* **2024**, *17*, 2701–2728. [CrossRef] [PubMed]
61. Shuster, J. Review: Cochrane handbook for systematic reviews for interventions, Version 5.1.0, published 3/2011. Julian P.T. Higgins and Sally Green, Editors. *Res. Synth. Methods* **2011**, *2*, 126–130. [CrossRef]
62. Kaur, M.N.; Cornacchi, S.D.; Tsangaris, E.; Poulsen, L.; Beelen, L.M.; Bordeleau, L.; Zhong, T.; Jorgensen, M.G.; Sorensen, J.A.; Mehrara, B.; et al. Iterative qualitative approach to establishing content validation of a patient-reported outcome measure for arm lymphedema: The LYMPH-Q Upper Extremity Module. *J. Patient Rep. Outcomes* **2024**, *8*, 63. [CrossRef]
63. Bakar, Y.; Tuğral, A.; Özdemir, Ö.; Duygu, E.; Üyetürk, Ü. Translation and Validation of the Turkish Version of Lymphedema Quality of Life Tool (LYMQOL) in Patients with Breast Cancer Related Lymphedema. *Eur. J. Breast Health* **2017**, *13*, 123–128. [CrossRef]
64. Aldridge, V.; Dovey, T.; Wade, A. Assessing Test-Retest Reliability of Psychological Measures. European Psychologist. *Eur. Psychol.* **2017**, *22*, 207–218. [CrossRef]
65. Pusic, A.; Liu, J.C.; Chen, C.M.; Cano, S.; Davidge, K.; Klassen, A.; Branski, R.; Patel, S.; Kraus, D.; Cordeiro, P.G. A systematic review of patient-reported outcome measures in head and neck cancer surgery. *Otolaryngol. Head. Neck Surg.* **2007**, *136*, 525–535. [CrossRef]
66. Hayes, S.; Cornish, B.; Newman, B. Preoperative assessment enables the early detection and successful treatment of lymphedema. *Cancer* **2010**, *116*, 260. [CrossRef]
67. Turgay, T.; Günel Karadeniz, P.; Maralcan, G. Quality of Life for Women with Breast Cancer-Related Lymphedema: The Importance of Collaboration between Physical Medicine and Rehabilitation and General Surgery Clinics. *Arch. Breast Cancer* **2021**, 119–126. [CrossRef]
68. Bulley, C.; Gaal, S.; Coutts, F.; Blyth, C.; Jack, W.; Chetty, U.; Barber, M.; Tan, C.W. Comparison of breast cancer-related lymphedema (upper limb swelling) prevalence estimated using objective and subjective criteria and relationship with quality of life. *Biomed. Res. Int.* **2013**, *2013*, 807569. [CrossRef] [PubMed]
69. The diagnosis and treatment of peripheral lymphedema: 2020 Consensus Document of the International Society of Lymphology. *Lymphology* **2020**, *53*, 3–19. [CrossRef]
70. Paramanandam, V.S.; Lee, M.J.; Kilbreath, S.L.; Dylke, E.S. Self-reported questionnaires for lymphoedema: A systematic review of measurement properties using COSMIN framework. *Acta Oncol.* **2021**, *60*, 379–391. [CrossRef]
71. Cormier, J.N.; Xing, Y.; Zaniletti, I.; Askew, R.L.; Stewart, B.R.; Armer, J.M. Minimal limb volume change has a significant impact on breast cancer survivors. *Lymphology* **2009**, *42*, 161–175.
72. Sanderson, J.; Tuttle, N.; Box, R.; Reul-Hirche, H.; Laakso, E.L. Localised Objective Characterisation Assessment of Lymphoedema (LOCAL): Using High-Frequency Ultrasound, Bioelectrical Impedance Spectroscopy and Volume to Evaluate Superficial Tissue Composition. *Diagnostics* **2024**, *14*, 1616. [CrossRef] [PubMed]
73. Lanza, M.; Bergmann, A.; Ferreira, M.G.; de Aguiar, S.S.; Dias Rde, A.; Abrahão Kde, S.; Paltrinieri, E.M.; Allende, R.G.; de Andrade, M.F. Quality of Life and Volume Reduction in Women with Secondary Lymphoedema Related to Breast Cancer. *Int. J. Breast Cancer* **2015**, *2015*, 586827. [CrossRef]

74. Viehoff, P.B.; van Genderen, F.R.; Wittink, H. Upper limb lymphedema 27 (ULL27): Dutch translation and validation of an illness-specific health-related quality of life questionnaire for patients with upper limb lymphedema. *Lymphology* **2008**, *41*, 131–138.
75. Bundred, N.; Foden, P.; Todd, C.; Morris, J.; Watterson, D.; Purushotham, A.; Bramley, M.; Riches, K.; Hodgkiss, T.; Evans, A.; et al. Increases in arm volume predict lymphoedema and quality of life deficits after axillary surgery: A prospective cohort study. *Br. J. Cancer* **2020**, *123*, 17–25. [CrossRef] [PubMed]
76. Ebbestad, F.E.; Ammitzbøll, G.; Horsbøll, T.A.; Andersen, I.; Johansen, C.; Zehran, B.; Dalton, S.O. The long-term burden of a symptom cluster and association with longitudinal physical and emotional functioning in breast cancer survivors. *Acta Oncol.* **2023**, *62*, 706–713. [CrossRef] [PubMed]
77. Teo, I.; Novy, D.M.; Chang, D.W.; Cox, M.G.; Fingeret, M.C. Examining pain, body image, and depressive symptoms in patients with lymphedema secondary to breast cancer. *Psychooncology* **2015**, *24*, 1377–1383. [CrossRef] [PubMed]
78. Stout, N.L.; Binkley, J.M.; Schmitz, K.H.; Andrews, K.; Hayes, S.C.; Campbell, K.L.; McNeely, M.L.; Soballe, P.W.; Berger, A.M.; Cheville, A.L.; et al. A prospective surveillance model for rehabilitation for women with breast cancer. *Cancer* **2012**, *118*, 2191–2200. [CrossRef]

12. DODATAK

Prilog 1. Odobrenje Etičkog povjerenstva Kliničkog bolničkog centra Split

KBC Split

KLINIČKI BOLNIČKI CENTAR SPLIT
ETIČKO POVJERENSTVO

Klasa: 500-03/23-01/42
Ur.broj: 2181-147/01/06/LJ.Z.-23-02

Split, 28.02.2023.

IZVOD
IZ ZAPISNIKA SJEDNICE ETIČKOG POVJERENSTVA KBC SPLIT 3/2023

22.

Doc.dr.sc Ana Poljičanin, dr.med, dr.med. iz Zavoda za fizikalnu medicinu i rehabilitaciju s reumatologijom KBC-a Split je uputila Etičkom povjerenstvu zamolbu za odobrenje provedbe istraživanja:

" Klinička, radiološka i laboratorijska obilježja subkliničkog limfedema ruke nastalog nakon provedenog liječenja karcinoma dojke "

Istraživanje za potrebe doktorske disertacije će se provesti u Zavodu za fizikalnu medicinu i rehabilitaciju s reumatologijom, Kliničkom zavodu za dijagnostičku i intervencijsku radiologiju, Zavodu za nuklearnu medicinu, Zavodu za plastičnu, rekonstruktivnu i estetsku kirurgiju i Klinici za onkologiju KBC-a Split. Suradnici u istraživanju su Ivana Klarić Kukuz, mag. physioth. Doktorand, doc. dr. sc. Jure Aljinović, dr. med., Barun Blaž, dr. med., Zdravko Divć, dr. med, doc. dr. sc. Danijela Budimir Mršić, dr. med., doc. dr.sc. Maja Marinović Guić, dr. med., Frano Šarić, dr. med., Tomislav Radović, dr. med., doc. dr. sc. Ana Barić, dr. med., Marko Vuletić, dr. med., izv. prof. Dr. sc. Vesna Boraska, doc. dr. sc. Marija Ban, dr.med., Goran Tintor, dr.med., Krešimir Bagatin, dr.med., Ivo Tripković, dr. med., doc. dr. sc. Tina Poklepović Perčić, doc. dr. sc. Ana Ćurković, dr. sc. Mario Marendić, mag. med. techn., i Ivana Grgić, bacc. physioth.

Nakon razmatranja zamolbe, donesen je sljedeći

Z a k l j u č a k

Iz priložene dokumentacije razvidno je da je Plan istraživanja usklađen s odredbama o zaštiti prava i osobnih podataka ispitanika iz Zakona o zaštiti prava pacijenata (NN169/04, 37/08) i Zakona o provedbi Opće uredbe o zaštiti podataka (NN 42/18), te odredbama Kodeksa liječničke etike i deontologije (NN55/08, 139/15) i pravilima Helsinške deklaracije WMA 1964-2013 na koje upućuje Kodeks.

Etičko povjerenstvo je suglasno i odobrava provođenje istraživanja.

PREDSJEDNIK ETIČKOG POVJERENSTVA
KLINIČKOG BOLNIČKOG CENTRA SPLIT
IZV.PROF. DR. SC. LJUBO ZNAOR