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Pooperacinių komplikacijų dažnis po laparoskopinių apendektomijų vaikams gydomiems Vilniuje ir sąsajos su rizikos veiksniais

The Frequency of Postoperative Complications After Laparoscopic Appendectomies and Their Relationship with Risk Factors in Children Treated in Vilnius

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TURINYS

1. SANTRAUKA

Tiriamojo darbo tikslas. Nustatyti ar komplikacijų dažnis po laparoskopinių apendektomijų vaikams gydomiems Vilniuje atitinka tarptautinius literatūroje pateiktus statistinius duomenis ir identifikuoti galimus rizikos veiksnius.

Tiriamieji ir metodai. Į tyrimą buvo įtraukiami 0 – 17 m. vaikai, sergantys ūminiu apendicitu ir ir hospitalizuoti chirurginiam gydymui Vilniaus Universiteto Santaros Klinikų vaikų chirurgijos skyriuje. Rinkti duomenys apie pacientų amžių, lytį, ūgį, svorį, kūno masės indeksą, simptomų pobūdį ir trukmę iki operacijos, atliktų laboratorinių (bendras kraujo tyrimas, c-reaktyvusis baltymas), instrumentinių (pilvo ultragarsas), mikrobiologinių (pasėlis iš pilvo ertmės), histologinių tyrimų rezultatus, laparoskopinės operacijos techniką (kelių troakarų ar vieno troakaro transumbilikalinė laparoskopija) bei trukmę. Tyrimo eigoje buvo registruojamos visos kilusios komplikacijos pooperaciniame periode pacientui gulint ligoninėje bei išvykus namo.

Rezultatai. Tyrime dalyvavo 81 berniukas ir 66 mergaitės (santykis 1,23:1). Vidutinis pacientų amžius 11,42 metai. Registruota 10 (6,8%) komplikacijų po laparoskopinės apendektomijos. Rastas statistiškai reikšmingas skirtumas tarp atvejų su kompikacijomis ir atvejų be komplikcijų analizuojant simptomų trukmę, absoliutų leukocitų skaičių, kirmėlinės ataugos diametrą, ultragarso tyrimo metu stebėtą laisvą skysčią, operacijos trukmę ir pacientų kūno masės indeksą.

Išvados. Komplikacijų skaičius Vilniaus Universiteto Santaros Klinikų vaikų chirurgijos skyriuje atitinka literatūroje pateiktus užsienio statistinius duomenimis. Svarbu paminėti, kad esame tarp mažiausiai kompikacijų turinčių ligoninių. Norint mažinti komplikacijų skaičių ateityje, reikia šviesti visuomenę apie galimus ūminio apendicito simptomus bei gerinti diagnostikos galimybes anksti diagnozuoti ligą ir skatinti gydytojus tobulinti laparoskopijos techniką įvairiuose mokymuose, kad reali operacija truktų kuo trumpiau.

Raktiniai žodžiai: ūminis apendicitas, laparokopinė apendektomija, postoperacinės komplikacijos, rizikos veiksniai.

2. SUMMARY

The aim of study. This study aimed to assess if the frequency of complications following laparoscopic appendectomies in children treated in Vilnius matches international statistical data and to indentify potential risk factors.

Subjects and Methods. Children (0-17 years) with acute appendicitis, hospitalized at Vilnius University Santaros Clinics' Pediatric Surgery Department, were studied. Data on age, gender, height, weight, symptoms pre-surgery, laboratory tests (WBC, CRP), imaging (ultrasound), microbiology (abdominal culture), histology, laparoscopic technique, and surgery duration were collected. Postoperative complications during hospitalization and after discharge were recorded.

Results. 81 boys and 66 girls participated (ratio 1.23:1), averaging 11.42 years. 10 complications (6.8%) were registered following laparoscopic appendectomy. A statistically significant difference was found between cases with complications and cases without complications when analyzing patients' body mass index (BMI), duration of symptoms, absolute leukocyte count, diameter of the appendix, free fluid observed during ultrasound examination and duration of surgery.

Conclusions. Complication rates in Vilnius align with international literature. Notably, the hospital ranks among those with fewer complications. To mitigate future complications, raising awareness about appendicitis symptoms, enhancing diagnostic capabilities for early detection, and encouraging laparoscopic training for physicians are crucial. These measures aim to enhance patient outcomes.

Keywords: acute appendicitis, laparoscopic appendectomy, postoperative complications, risk factors.

3. ĮVADAS

Ūmus apendicitas yra dažniausia vaikų chirurginė pilvo skausmo priežastis. Iš visų vaikų, besikreipiančių į skubios pagalbos skyrių, ūmus apendicitas diagnozuojamas 1-8% atvejų (1). Didžiausia susirgimo rizika pasireiškia antrajame gyvenimo dešimtmetyje, tuo tarpu apendicito atvejai jaunesniems kaip 5 metų vaikams aprašomi rečiau. Tačiau, svarbu paminėti, kad apendicitu susirgti gali ir naujagimiai (2). Pagrindinis ligos požymis yra migruojantis pilvo skausmas, kuris prasideda epigastrium ar bambos srityse ir per pirmą sirgimo parą nusileidžia į dešinįjį apatinį pilvo kvadrantą. Pilvo skausmą gali lydėti pykinimas, vėmimas, karščiavimas. Jaunesniems vaikams apendicitas neretai pasireiškia netradicine klinika (3).

Laparoskopinė apendektomija šiuo metu yra laikoma standartiniu ūminio apendicito gydymo metodu (4). Gydymo rezultatas gali priklausyti nuo įvairių veiksnių: ligos sudėtingumo, sirgimo laiko, operacijos technikos bei jos trukmės. Literatūroje pateikiami skirtingi galimi rizikos veiksniai pooperacinėms komplikacijoms (5,6).

Lietuvoje ūminiu apendicitu susirgusiems vaikams taip pat atliekama skubi laparoskopinė apendektomija: apie 1000 operacijų per metus. Kitų valstybių duomenimis, bendras pooperacinių komplikacijų dažnis po laparoskopinių apendektomijų varijuoja nuo 5% iki 25%, tačiau iki šiol literatūroje nėra aprašytas Lietuvos, kaip atskiros šalies, bendras pooperacinių komplikacijų skaičius. Kalbėdami su pacientais bei jų tėvais, mūsų šalies gydytojai remiasi užsienio duomenimis. Informacija apie operacijų skaičių, kuomet po atliktos procedūros nepasireiškia nei viena komplikacija, taip pat pačių komplikacijų dažnį ir pasiskirstymą Lietuvoje išlieka nežinoma. Šią statistiką savo šalyje svarbu žinoti taip pat ir siekiant identifikuoti tas komplikacijas, kurių skaičių būtų galima ir reikėtų mažinti ateityje.

Praktinė tiriamojo darbo reikšmė: Atlikto tyrimo rezultatai parodys, kiek ir kokių komplikacijų būna po laparoskopinių apendektomijų Vilniuje gydomiems vaikams. Taip pat bus ištirta, kokie yra komplikacijų galimi rizikos veiksniai. Žinant savo komplikacijų galimas priežastis, ateityje būtų galima ieškoti būdų, kaip sumažinti konkrečius skaičius savo šalyje.

Tiriamojo darbo tikslas: Nustatyti ar komplikacijų dažnis po laparoskopinių apendektomijų vaikams gydomiems Vilniuje atitinka užsienio literatūroje pateiktus statistinius duomenis.

Tiriamojo darbo uždaviniai:

1. Nustatyti laparoskopinių apendektomijų be pasireiškusių komplikacijų pooperaciniame periode dažnį vaikams Vilniaus tretinio lygio ligoninėje;

2. Nustatyti komplikacijų po laparoskopinių apendektomijų dažnį vaikams ir palyginti gautus rezultatus su užsienio literatūra;

3. Identifikuoti galimus rizikos veiksnius komplikacijoms po laparoskopinių apendektomijų vaikams.

4. METODAI

Atliktas perspektyvusis stebėsenos ir retrospektyvinis apžvalginis vieno centro tyrimas Vilniaus Universiteto ligoninėje Santaros Klinikos, Vaikų Chirurgijos, Ortopedijos ir Traumatologijos centre. Tyrimui atlikti gautas Vilniaus regioninio biomedicininių tyrimų etikos komiteto leidimas *Nr. 2023/9-1535-992*. Analizuojant komplikacijų galimus rizikos veiksnius buvo panaudoti papildomi duomenys iš anksčiau atlikto tyrimo, kurio Vilniaus regioninio biomedicininių tyrimų etikos komiteto leidimo *Nr. 2019/3-1114-607.*

4.1. Tiriamieji

Apskaičiuoti pooperacinių komplikacijų dažnį į šį tiriamąjį darbą įtraukiami asmenys buvo vaikai (0 – 17m.), sergantys ūmiu apendicitu ir hospitalizuoti chirurginiam gydymui Vilniaus Universiteto Santaros Klinikų vaikų chirurgijos skyriuje. Pacientų įtraukimo ir atmetimo kriterijai pateikiami lentelėje **(1 lentelė).** Tiriamieji buvo renkami 7 mėnesius (2023 / 2024) nuo tyrimo pradžios. Per šį laikotarpį buvo renkami visi pacientai atitinkantys įtraukimo ir atmetimo kriterijus. Tačiau, siekiant surinkti didesnę pacientų su pasireiškusiomis pooperacinėmis komplikacijomis grupę, į tyrimą papildomai įtraukti 2019 – 2022 skyriuje dėl ūminio apendicito operuoti vaikai, kurie atitiko biomedicininio tyrimo kriterijus ir kurių elektroninėse ligos istorijose registruotos komplikacijos.

1 lentelė. *Pacientų įtraukimo ir atmetimo kriterijai.*

Įtraukimo kriterijai
Diagnozuotas ūminis apendicitas (katarinis/ flegmoninis/ gangreninis/ perforacinis su ar be peritonito)
Atlikta laparoskopinė apendektomija
Amžius nuo 0 iki 17m.
Pasirašyta informuoto asmens sutikimo forma

Atmetimo kriterijai
Diagnozuotas lėtinis apendicitas
Atlikta atvira apendektomija
Sunkios gretutinės infekcijos, imunosupresinės būklės

4.2. Tyrimo eiga

Tyrimo metu naudotas standartinis ūminio apendicito diagnostikos ir gydymo protokolas 21-V-547. Pacientai į tyrimą įtraukti po atliktos laparoskopinės apendektomijos. Papildomų vizitų tyrimo tikslais nebuvo.

Pacientų tėvams pasirašius informuoto asmens sutikimo formas, buvo renkama visa tyrimui reikalinga informacija iš pacientų, jų tėvų bei elektroninių ligų istorijų. Rinkti duomenys apie pacientų amžių, lytį, ūgį, svorį, kūno masės indeksą, simptomų pobūdį ir trukmę iki operacijos, atliktų laboratorinių (BKT, CRB), instrumentinių (pilvo ultragarsas), mikrobiologinių (pasėlis iš pilvo ertmės), histologinių tyrimų rezultatus, laparoskopinės operacijos techniką (kelių troakarų ar vieno troakaro transumbilikalinė laparoskopija) bei trukmę. Taip pat surinkti tėvų kontaktiniai telefono numeriai. Duomenys rinkti naudojant Microsoft Excel programą.

Pacientai po operacijų buvo prižiūrimi pagal standartinę tvarką ir išleidžiami namo pagal ligoninės numatytus kriterijus ir terminus. Tyrimo eigoje buvo registruojamos visos kilusios komplikacijos pooperaciniame periode pacientui gulint ligoninėje bei išvykus namo (susisiekus su jo tėvais telefonu du kartus: pirmą kartą po 2-4 sav.; antrą kartą praėjus dar 6-8 sav.).:

1. Kraujavimas, hematomos;
2. Įvairaus laipsnio chirurginių žaizdų paviršinių ir giliųjų audinių infekcijos;
3. Pooperacinės bambos granuliomos;
4. Intraabdominaliniai pooperaciniai infiltratai arba dubens srities abscesai;
5. Mechaninis (sąaugiminis) žarnų nepraeinamumas;
6. Žarnų obstrukcija, žarnyno disfunkcija, obstipacijos;
7. Peritonitas dėl kirmėlinės ataugos bigės mazgo atsilaisvinimo;

Papildomai panaudoti ankstesnio tyrimo su apendicitais nuasmeninti duomenys. Atsižvelgiant į tyrimo įtraukimo ir atmetimo kriterijus atrinkti tie pacientai, kuriems pasireiškė

komplikacijos po laparoskopinės apendektomijos ir šių pacientų duomenys reikalingi šiam tyrimui. Duomenų rinkimui ir laikymui taip pat buvo naudojama Microsoft Excel programa.

Pacientai buvo suskirstyti į 2 grupes: su pasireiškusiomis komplikacijomis po laparoskopinės apendektomijos ir be pasireiškusių postoperacinių komplikacijų.

4.3. Statistinė duomenų analizė

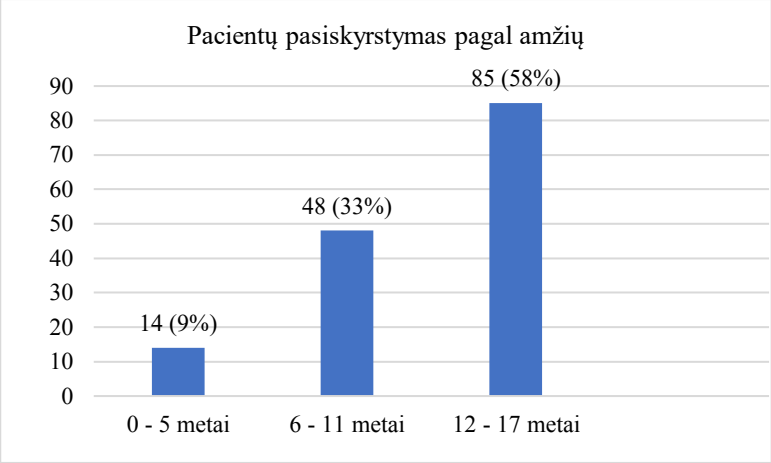
Surinkti duomenys apdoroti ir analizuoti su "Microsoft Excel" ir "IBM SPSS 23 for Mac". Kokybiniams kintamiesiems aprašyti naudojami absoliutūs duomenų skaičiai (n) ir jų procentinė išraiška (%). Kiekybinių kintamųjų rezultatai aprašomi vidurkį ir standartinį nuokrypį (SD). Kintamųjų reikšmių vidurkiai tiriamosiose dviejose nepriklausomose grupėse lyginti taikant parametrinį Stjudento t kriterijų nepriklausomoms populiacijoms. Tiesinio ryšio stiprumas tarp kintamųjų apskaičiuotas taikant Pirsono koreliacijos koficientą. Tyrime statistinio reikšmingumo lygmuo pasirinktas a=0,05, požymių priklausomybės ir skirtumai laikyti statistiškai reikšmingais, kai $p<0,05$.

5. REZULTATAI

5.1. Bendroji dalis

Per 7 mėnesius (2023 / 2024), pacientų įtraukimo į tyrimą laikotarpį, Vilniaus Universiteto Santaros Klinikų vaikų chirurgijos skyriuje dėl ūminio apendicito operuoti 151 vaikai. Remiantis įtraukimo ir atmetimo kriterijais tyrimui atrinkti 147 pacientai: 2 vaikų nebuvo galima įtraukti dėl sunkių gretutinių ligų, kitiems 2 vaikams atlikta atvira apendektomija.

Į tyrimą įtraukti 81 (55%) berniukai ir 66 (45%) mergaitės (santykis 1,23:1). Vidutinis pacientų amžius 11,42 (SD ± 3.581) metų. Pagal amžiaus grupes pacientai pasiskirstė taip: 0 – 5 metų amžiaus grupėje buvo 14 (9%) vaikų, 6 – 11 metų amžiaus grupėje gydyti 48 (33%) vaikai ir daugiausiai pacientų stebėta 12 – 17 metų amžiaus grupėje, jai priklausė 85 (58%) vaikai **(1 paveikslas).** Vidutinis pacientų kūno masės indeksas (KMI) 18.59 (SD ± 3.582). 6 (4%) vaikams nustatytas antsvoris (KMI > 25), iš kurių vieno vaiko KMI siekė nutukimo lygį (KMI > 30).



1 pav. *Pacientų pasiskirstymas skirtingose amžiaus grupėse.*

Iki operacijos pacientai sirgo ir skundėsi simptomais vidutiniškai 28,9 (SD ± 15.011) valandas. 0 – 5 metų amžiaus grupėje ūminį apendicitą diagnozuoti užtrukdavo ilgiau (vidutiniškai 45.8 val.) lyginant su vyresnėmis amžiaus grupėmis 6 – 11 m. (vidutiniškai 27,7 val.) ir 12 – 17 m. (vidutiniškai 26,7 val.). Pilvo skausmu skundėsi visi pacientai, 71 (48%) vaikui stebėtas lokalus ar difuzinis raumenų tempimas bei pilvaplėvės dirginimo požymiai. 105 (71%) pacientams pasireiškė pykinimas, 85 (58%) vėmimas, 62 (42%) karščiavimas. 35 (24%) pacientai teigė vartoję vaistus nuo skausmo (ibuprofeną, NO-SPA), temperatūros (paracetamolį), pykinimo (aktyvintąją anglį), tačiau tik 5 pacientams vaistų vartojimas turėjo trumpalaikį teigiamą efektą, kiti pacientai simptomų sumažėjimo po vaistų vartojimo nestebėjo.

137 (93%) pacientams atliktas bendras kraujo tyrimas: neutrofilinė leukocitozė stebėta 123 pacientams. Apskaičiuota vidutinė leukocitų reikšmė absoliučiais skaičiais 15,9 x 10^9/l, tuo tarpu vidutinė neutrofilų reikšmė – 13,13 x 10^9/l. C – reaktyvaus baltymo (CRB) tyrimas atliktas 131 (89%) pacientams ir 92 (63%) pacientams buvo nustatyta padidėjusi CRB reikšmė (CRB > 5 mg/l). Vidutinė visų atliktų CRB tyrimų reikšmė gauta 31,6 mg/l. Vaikų priėmimo-skubios pagalbos ar vaikų chirurgijos skyriuje 125 (85%) pacientams atliktas pilvo ultragarsinis (UG) tyrimas prieš apendektomiją. Tyrimo metu sustorėjusi kirmėlinė atauga (KA) rasta 107 (73%) vaikams, vidutinis KA diametras 9.9 mm (SD ± 2.322). Laisvas skystis UG metu stebėtas 57 (39%) atvejams. Tarp skirtingų amžiaus grupių laboratorinių ir instrumentinių tyrimų duomenys pasiskirstė panašiai.

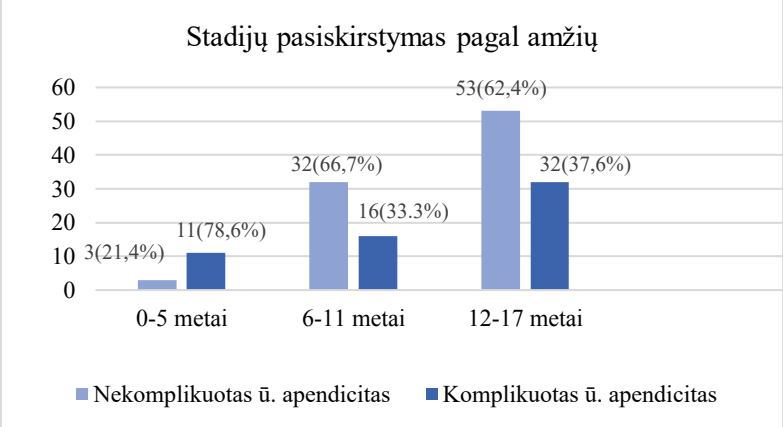
Buvo peržiūrėtos operacijos metu, vertinant makroskopinius KA patologinius požymius, nustatytos ūminio apendicito stadijos ir sulygintos su histologinių tyrimų atsakymais. Apskaičiuota, kad 25% atvejų diagnozės nesutampa, todėl šiame tyrime ūminio apendicito

stadijų duomenys analizuojami pagal histologinių tyrimų vertinimą. Daugiausiai rasta flegmoniškai pakitusių apendiksų – 69 (47%). Katarinis apendicitas nustatytas 19 (13%) atvejams, gangreniniai KA pokyčiai vizualizuoti 47 (32%) vaikams, o gangreninė perforacinė stadija nustatyta 12 (8%) atvejų. Katarinio ir flegmoninio ūminio apendicito stadijos laikomos nekomplikuotais apendicitais, tuo tarpu gangreninė bei perforacinė stadijos – komplikuotais. Ūminio apendicito stadijų pasiskirstymas pateiktas **2 lentelėje.**

2 lentelė. *Ūminio apendicito pasiskirstymas pagal stadiją.*

STADIJA	Pacientų sk. (%)
Nekomplikuotas ūminis apendicitas	**88 (60)**
Katarinis	19 (13)
Flegmoninis	69 (47)
Komplikuotas Ūminis apendicitas	**59 (40)**
Gangreninis	47 (32)
Gangreninis su perforacija	12 (8)

Komplikuotų ir nekomplikuotų ūminių apendicitų pasiskirstymas skirtingose amžiaus grupėse parodytas **2 paveiksle.** Jaunesniems nei 5 metų amžiaus vaikams daug dažniau diagnozuota komplikuota ūminio apendicito stadija (78,6%), tuo tarpu vyresnėse amžiaus grupėse (6 – 11 m. ir 12 -17 m.) dažniau diagnozuota nekomplikuota stadija. Ryškaus pasiskirstymo skirtumo tarp šių dvejų grupių nestebėta.



2 pav. *Nekomplikuotų ir komplikuotų ūminio apendicito stadijų pasiskirstymas tarp skirtingų amžiaus grupių.*

Visiems į tyrimą įtrauktiems pacientams atlikta laparoskopinė apendektomija. Vidutinė operacijos trukmė buvo 52 minutės (SD ± 16.96). Per vieną troakarą (transumbilikalinė laparoskopija – TULA) atliktos 48 operacijos (33%). Operacijos vidutinė trukmė šioje pacientų grupėje buvo 40 minučių, tuo tarpu standartinės laparoskopijos per 2 ar 3 troakarus vidutinė trukmė ilgesnė – 57 minutės. Vieno troakaro ir kelių troakarų operacijų trukmės skiriasi statistiškai reikšmingai ($p < 00.5$). TULA operacijos būdu operuoti 40 nekomplikuoti ir 8 komplikuoti apendicitai, taigi TULA dažniausiai taikoma nekomplikuotų apendicitų grupėje. Po operacijos vaikų hospitalizacija skyriuje truko vidutiniškai 5,4 dienas (SD ± 3.458). Lyginant hospitalizacijos trukmes tarp skirtingų operacijos metodų taip pat gautas statistiškai reikšmingas skirtumas ($p < 00.5$), vidutinės hospitalizacijos trukmės po standartinės laparoskopijos ir TULA atitinkamai buvo 6,22 ir 3,75 dienos. Tačiau ilgesniam vaikų gulėjimui stacionare po operacijos įtakos gali turėti ne tik operacijos metodas, bet ir tai, jog standartinės laparoskopijos metu dažniau operuojami komplikuoti apendicitai, kurie įprastai gyja ilgiau. Pacientų amžius ir kirmėlinės ataugos diametras UG tyrimo metu statistiškai reikšmingai nesiskyrė tarp skirtingų operacijos metodų **(3 lentenlė).**

3 lentelė. *Standartinės ir transumibilikalinės (TULA) laparoskopijų palyginimas.*

	Standartinė laparoskopija	**TULA**	**p reikšmė**
Komplikuotų apendicitų skaičius	51	8	**<0.005**
Vidutinis pacientų amžius (metai)	11.5	11.27	0.723
Vidutinis KMI	19.1	17.6	**0.019**
Vidutinis KA diametras (mm)	9.96	9.85	0.812
Vidutinė operacijos trukmė (min.)	57	40	**<0.005**
Vidutinė hospitalizacijos trukmė (d.)	6.22	3.75	**<0.005**

Operacijos metu 46 (31%) pacientams imtas pasėlis iš pilvo ertmės mikrobiologiniam ištyrimui, iš jų 35-iems rastas bakterijų augimas. Dažniausiai pasėlyje stebėtas *Escherichia coli* (29)*, Streptococcus anginosus* ir *Bacteroides fragilis* bakterijų augimas. *Pseudomonas aeruginosa* bakterijos išaugo 7 pacientų pasėliuose.

58 pacientai po operacijos karščiavo. Jų vidutinis karščiavimo laikas buvo 2.3 paros. Apskaičiuotas ir visų pacientų vidutinis karščiavimo po operacijos laikas, įskaitant ir tuos, kurie po operacijos nekarščiavo, gauta 0.9 paros. Antibiotikoterapija po operacijos skirta 59

(40%) pacientams. Dažniausiai po laparoskopinės apendektomijos pacientams skirta monoterapija amoksiklavu.

Atvejų, kuomet po laparoskopinės apendektomijos nepasireiškė nei viena komplikacija, tyrimo metu buvo 137 iš 147 (93,2%). Toliau duomenys buvo analizuojami ir lyginami tarpusavyje atskirose pacientų grupėse: atvejai be komplikacijų ir atvejai su pasireiškusiomis komplikacijomis.

5.2. Komplikacijos po laparoskopinės apendektomijos

Tyrimo laikotarpiu iš viso registruota 10 (6,8%) komplikacijų po laparoskopinės apendektomijos vaikams gydomiems Vilniaus Universiteto Santaros Klinikų vaikų chirurgijos skyriuje. Stacionarinio gydymo metu 2 vaikams po operacijos susiformavo poapendicitiniai pilvo ertmės pūliniai. 2 pacientai buvo pakartotinai hospitalizuoti dėl susidariusių poapendicitinių infiltratų. 4 pacientai skundėsi operacinės žaizdos supūliavimu ir 2 pacientai kreipėsi į polikliniką dėl susidariusių pooperacinių bambos granuliomų. Komplikacijos pasireiškė 6 pacientams, kuriems buvo diagnozuota komplikuota ūminio apendicito stadija (gangreninis / gangreninis perforacinis) ir 4 pacientams, kuriems diagnozuota nekomplikuota stadija (katarinis / flegmoninis) **(lentelė 4).**

4 lentelė. *Komplikuotų ūminių apendicitų stadijų pasiskirstymas tarp pooperacinių komplikacijų.*

Komplikacija	Pacientų sk.	Nekomplikuotų apendicitų sk.	Komplikuotų apendicitų sk.
ANKSTYVOS (pasireiškusios hospitalizacijos metu)			
Poapendicitinis pūlinys	2	0	2
VĖLYVOS (pasireiškusios išvykus iš stacionaro)			
Operacinės žaizdos infekcija	4	2	2
Pooperacinė bambos granulioma	2	1	1
Poapendicitinis infiltratas	2	1	1

Vaikų grupėje, kurioje registruotos pooperacinės komplikacijos, vidutinis pacientų amžius buvo 11,6 (SD ± 3.864). 4 berniukai ir 6 mergaitės, komplikacijų dėsningumo pasiskirstant tarp lyčių, kuomet vienai lyčiai būtų būdinga tam tikros komplikacijos didesnis

išsivystymo dažnis, nestebėta. Vidutinis pacientų KMI siekė 20.26 (SD ± 4.421), 1 pacientui nustatytas antsvoris, 1 pacientui – nutukimas. Šios grupės vaikai iki operacijos simptomais skundėsi vidutiniškai 29,2 (SD ± 14.274) valandas. Vidutinis KA diametras UG tyrimo metu siekė 9.68 (SD ± 2.676), laisvas skystis rastas 2 pacientams. Visos laparoskopinės apendektomijos šiems vaikams atliktos naudojant 2 troakarus, vidutinė operacijos trukmė – 53 minutės (SD ± 17.029). Dėl susidariusių pooperacinių pilvo ertmės pūlinių, 2 pacientai stacionare gydyti 10 ir 24 dienas atitinkamai. Kitų šios grupės pacientų vidutinė hospitalizacijos trukmė 4,5 dienos. Statistiškai reikšmingo skirtumo tarp atvejų su pasireiškusiomis komplikacijomis ir be komplikacijų nebuvo rasta lyginant pacientų amžių, vidutinį KMI, simptomų trukmę, vidutinį KA diametrą, vidutinę operacijos ir hospitalizacijos trukmę **(5 lenetelė).**

5 lentelė. *Atvejų su pasireiškusiomis komplikacijomis ir atvejų be pasireiškusių komplikacijų palyginimas.*

	Atvejai su pasireiškusiomis komplikacijomis	**Atvejai be komplikacijų**	**p reikšmė**
Vidutinis pacientų amžius (metai)	11.6	11.4	0.871
Vidutinis KMI	20.26	18.46	0.13
Simptomų trukmė (val.)	29.2	28.84	0.942
Vidutinis KA diametras (mm)	9.68	9.95	0.743
Vidutinė operacijos trukmė (min.)	53	51.7	0.818
Vidutinė hospitalizacijos trukmė (d.)	6.4	5.3	0.134

Tyrimo metu komplikacijų gauta mažiau nei tikėtasi (6,8%), pacientų grupė su pasireiškusiomis komplikacijomis gavosi per maža apskaičiuoti statistiškai patikimas sąsajas su rizikos veiksniais. Dėl to, retrospektyviai peržiūrėti 2019 – 2022 metų rinkti duomenys apie pacientus, kuriems nustatyta ūminio apendicito diagnozė ir papildomai atrinkti 45 pacientai su pasireiškusiomis komplikacijomis po laparoskpinės apendektomijos. Sudaryta nauja pacientų su komplikacijomis grupė (55 pacientai).

5.3. Galimi rizikos veiksniai pooperacinėms komplikacijoms

Naujai sudarytoje vaikų grupėje su pasireiškusiomis komplikacijomis (55 pacientai) įtraukti 4 (7%) operacinių žaizdų supūliavimai, 2 (4%) susidariusiusios pooperacinės bambos granuliomos, 16 (29%) pooperacinių apendikuliarinių pūlinių ir 33 (60%) pooperaciniai infiltratai. Didžioji atvejų dalis (49 pacientai, 89%) – komplikuoti ūminiai apendicitai, iš kurių 14 gangreninių ir 35 gangreniniai su perforacija. Vidutinis pacientų amžius buvo 10,7 (SD ± 3.217). 32 (58,2%) berniukai ir 23 (41,8%) mergaitės. Komplikacijų išsivystymo priklausomybės nuo amžiaus ar lyties nestebėta **(6 lentelė).** Vidutinis pacientų KMI siekė 20.02 (SD ± 4.506), 2 pacientams nustatytas antsvoris, 3 pacientams – nutukimas. Šios grupės vaikai iki operacijos simptomais skundėsi vidutiniškai 41,6 (SD ± 18.705) valandas. Vidutinis KA diametras UG tyrimo metu siekė 11.75 (SD ± 2.623), laisvas skystis rastas 30 (55%) pacientų. Vidutinė operacijos trukmė pacientų grupėje su komplikacijomis nustatyta ženkliai ilgesnė – 76 minutės. Laparoskopinė apendektomija pacientams atlikta standartiniu metodu 49 (89%) pacientams, tuo tarpu TULA (11%) atlikta 6 pacientams. Statistiškai reikšmingas skirtumas tarp atvejų su pasireiškusiomis kompikacijomis ir be pasireiškusių komplikacijų buvo rastas lyginant pacientų vidutinį KMI, simptomų trukmę, vidutinį KA diametrą, UG metu stebėtą laisvą skystį, vidutinę operacijos trukmę, vidutinį leukocitų skaičių ir vidutinę CRB reikšmę **(6 lentelė).**

6 lentelė. *Atvejų su pasireiškusiomis komplikacijomis (nauja grupė) ir atvejų be pasireiškusių komplikacijų palyginimas.*

	Atvejai su pasireiškusiomis komplikacijomis	**Atvejai be komplikacijų**	**p reikšmė**
Vidutinis pacientų amžius (metai)	10.7	11.4	0.221
Berniukų/mergaičių santykis	1.39:1	1.28:1	0.804
Vidutinis KMI	20.02	18.46	**0.032**
Simptomų trukmė (val.)	41.6	28.84	**<0.05**
Vidutinis KA diametras (mm)	11.75	9.95	**<0.05**
UG metu stebėtas laisvas skystis (pacientų sk.)	30	55	**0.0353**
Vidutinė operacijos trukmė (min.)	76	51.7	**<0.05**

Vidutinis leukocitų skaičius	17.68	15.97	**0.045**
Vidutinis neutrofilų skaičius	14.81	13.2	0.2
Vidutinė CRB reikšmė	86.2	32.93	**<0.05**

Ientifikavus, kurie rizikos veiksniai statistiškai reikšmingai skiriasi tarp atvejų grupės be komplikacijų ir grupės su komplikacijomis, nustatytas šių veiksnių kintamųjų tiesinio ryšio stiprumas taikant Pirsono koreliacijos koficientą. Komplikacijų išsivystymas turi labai silpną ryšį su pacientų KMI (r=0.164, p=0.032), laisvu skysčiu UG metu (r=0.171, p=0.035) bei leukocitų skaičiumi (r=0.150, p=0.045). Silpna koreliacija nustatyta tarp komplikacijų išsivystymo ir simptomų trukmės (r=0.336, p<0.05), KA diametro (r=0.314, p<0.05), operacijos trukmės (r=0.041, p<0.05) ir CRB reikšmės (r=0.440, p<0.05). Galutinę ligos diagnozę (ūminio apendicito stadija) ir komplikacijų išsivystymą sieja vidutinio stiprumo ryšis (r=0.560, p<0.05) **(7 lentelė).** Stiprios koreliacijos analizuojant mūsų tyrimo duomenis negauta. Visi rizikos veiksniai yra labai glaudžiai susiję tarpusavyje, kuo ilgesnė simptomų trukmė, tuo labiau vystosi ūminis apendicitas, blogėja stadija, gali įvykti perforacija ir pūliams patekus į pilvo ertmę ženkliai padidėja uždegiminiai rodikliai. Galbūt dėl to analizuojant kiekvieną rodiklį atskirai gauti pakankamai maži koreliacijos koficientai ir komplikacijų išsivystymą lemia kelių skirtingų rizikos veiksnių kombinacijos.

7 lentelė. *Komplikacijų išsivystymo rizikos tiesinio ryšio stiprumas.*

	KMI	Simptomų trukmė	KA diametras	Laisvas skystis UG	Operacijos trukmė	Leukocitų skaičius	CRB skaičius	Galutinė diagnozė (katarinis, flegmoninis, gangreninis, perforacija)
Pirsono koreliacijos koeficientas (r)	0.164	0.336	0.314	0.171	0.421	0.150	0.440	**0.560**
Statistinis patikimumas (p)	0.032	.000	.000	0.035	.000	0.045	.000	.000

41 pacientų komplikacijos (poapendikuliarinis pūlinys ar poapendikuliarinis infiltratas) registruotos dar hospitalizacijos metu, dėl kurių pacientai skyriuje gydyti ilgiau, vidutinė visos grupės hospitalizacijos trukmė 13 dienų. Komplikacijų priklausomybė nuo hospitalizacijos

trukmės nebuvo analizuojama, kadangi didžioji dalis komplikacijų pasireiškė dar hospitalizacijos metu.

6. APTARIMAS

6.1. Ūminis apendicitas

Ūminis apendicitas yra visų laikų dažniausia ūmi vaikų chirurginė liga, daugiausiai pasireiškianti antrajame gyvenimo dešimtmetyje. Jungtinėse Amerikos Valstijų duomenimis ūminio apendicito sergamumo dažnis tarp vaikų nuo gimimo iki 4 metų amžiaus yra 1-2 atvejai 10 000 vaikų, tuo tarpu 10 – 17 amžiaus grupėje sergamumas padidėja iki 25 atvejų 10 000 vaikų per metus (7). Lietuvoje apendektomijų vaikams atliekama apie 1000 kartų per metus (Higienos Instituto duomenimis). Remiantis oficialiosios statistikos portalo duomenimis, 2024 metų pradžioje Lietuvoje registruota 502 892 vaikai, taigi mūsų šalies vaikų sergamumas ūminiu apendicitu siekia apie 20 atvejų 10 000 vaikų per metus, paaugliai taip pat serga dažniau negu ikimokyklinio amžiaus vaikai. Dėl didelio sergamumo ūminio apendicito tema išlieka aktuali siekiant gerinti gydymo rezultatus ir palikti kuo įmanoma mažesnį pooperacinį randą. Literatūros duomenimis, apendicitu dažniau serga berniukai negu mergaitės (santykiu 1,4:1) (8), šiame tiriamajame darbe lyčių santykis gautas labai panašus – 1,23:1.

Pagrindine ūminio apendicito priežastimi yra laikoma kirmėlinės ataugos spindžio obstrukcija. Ypač retais atvejais ūminį apendicitą gali sukelti buka pilvo trauma dėl tiesioginio spaudžiančio apendikso sužalojimo ar jo spindžio suspaudimo ileocekaline hematoma (9,10). Kirmėlinės ataugos obstrukciją gali sukelti kaprolitai, svetimkūniai, daržovių ar vaisių sėklos, žarnyno parazitai (*Entamoeba, Strongyloides, Enterobius vermicularis* ir kt.), limfinio audinio hiperplazija dėl bakterinių (*Yersinia, Salmonella*, *Shigella* ir kt.) ar virusinių infekcijų (enterovirusas, citomegalovirusas, tymai, vėjaraupiai ir kt.), pirminiai navikai (karcinoidas, adenokarcinoma, Kapoši sarkoma, limfoma), metastazės (9,11).

Yra pasiūlytos kelios ūminio apendicito klasifikacijos. Geriausiai žinoma ir plačiausiai naudojama klasifikacija remiasi makroskopiniu chirurginių radinių vertinimu bei histopatologiniais pokyčiais ir yra skirstoma į keturias stadijas: katarinė, flegmoninė, gangreninė ir perforacinė **(8 lentelė)** (12–14).

8 lentelė. *Ūminio apendicito stadijų makroskopiniai ir mikroskopiniai pokyčiai.*

Ūminio apendicito stadija	**Makroskopinis KA vaizdas**	**Histologiniai KA pokyčiai**
Katarinis	Nesiskiria nuo sveiko apendikso	Neutrofilinė infiltracija KA gleivinėje ir spindyje, pavieniai gleivinės išopėjimai
Flegmoninis	padidėjęs KA diametras, išsiplėtusios kraujagyslės, fibropurulentinis eksudatas	neutrofilinė infiltracija KA gleivinėje, pogleivyje bei savajame raumeniniame sluoksnyje, difuziniai gleivinės išopėjimai, tarpsieniniai abscesai, kraujagyslių trombozė
Gangreninis	KA spalva pakitusi į tamsiai violetinę, žalią ar juodą	nekrozinės zonos KA sienelėje, difuziniai išopėjimai
Gangreninis su perforacija	KA perforacija, pūliai pilvo ertmėje, aplinkinių audinių uždegiminiai pokyčiai	nekrozinės zonos KA sienelėje, difuziniai išopėjimai, perforacija

Taip pat, ūminis apendicitas skirstomas į komplikuotus ir nekomplikuotus, tačiau komplikuoto apendicito apibrėžimas literatūroje šiek tiek varijuoja. KA perforacija, lokalus ar difuzinis peritonitas, periapendikuliariniai pūliniai vieningai laikomi komplikuotu apendicitu, tuo tarpu gangreninis ūminis apendicitas ne visose studijose yra įtraukiamas į minėtą grupę (15–17). Šiame biomedicininiame tyrime gangreninė ūminio apendicito stadija buvo laikoma komplikuotu apendicitu. Komplikuoti apendicitai literatūros duomenimis sudaro apie 30% visų ūminio apendicito atvejų (18). Tülin Öztaş ir bendraautoriai lygino komplikuotų apendicitų (įskaitant ir gangreninius) skaičių prieš COVID pandemiją bei pandemijos metu ir nustatė, kad komplikuotų atvejų procentas panašus abejose grupėse, atitinkamai, 37,5% ir 31,9% (19). Mūsų atliktame tyrime komplikuotų apendicitų skaičius siekia 40%. Procentas gali būti šiek tiek didesnis nei literatūroje pateikiamas vidurkis, nes tiriamieji buvo gydomi tretinio lygio centre, į kurį pervežami ir visi sunkesni atvejai iš aplinkinių regioninių ligoninių.

Ūminio apendicito pagrindinis simptomas yra pastovus pilvo skausmas, dažnai prasidedantis epigastriumo srityje arba apie bambą, vėliau, dažniausiai per 24 val. nuo skausmo pradžios, migruojantis į dešinę klubinę sritį. Ši skausmo migracija dar vadinama teigiamu

Kocherio simptomu (20). Skausmas intensyvėja judant, pavyzdžiui einant ar važiuojant automobiliu per kelio nelygumus. Kiti dažnai pasitaikantys ūminio apendicito simptomai: pykinimas, vėmimas bei apetito stoka. Rečiau pasitaiko viduriavimas ar vidurių užkietėjimas (21). Subfebrilus karščiavimas gali lydėti nekomplikuotą ūminį apendicitą, tuo tarpu įvykus perforacijai būdinga febrili kūno temperatūra. Pilvo skausmas kartu su vėmimu ir karščiavimu būna iki 60% pacientų su ūminiu apendicitu (22). Palpacijos metu gali būti jaučiamas lokalus raumenų tempimas dešinėje klubinėje srityje, teigiami pilvaplėvės dirginimo simptomai: teigiamas Rovsingo požymis (skausmas dešinėje klubinėje srityje palpuojant kairiąją), Bliumbergo simptomas (tolygiai spaudžiant dešinėje klubinėje srityje ir staigiai atitraukus ranką labiau suskausta rankos atitraukimo metu) (23). Pilvo skausmu skundėsi visi (100%) šio biomedicininio tyrimo pacientai, o minėta simptomų triada (pilvo skausmas, vėmimas, karščiavimas) pasireiškė 27% pacientų. Naujagimiams ir vaikams iki 5 metų ūminio apendicito klinika dažnai būna netipinė, dėl to šioje amžiaus grupėje dažniau diagnozuojami jau komplikuoti ūminiai apendicitai (2,3). Dažniausias simptomas mažiems vaikams būna vėmimas, kuris pasitaiko apie 90% atvejų, pilvo skausmas lydi tik 35 – 80% atvejų, karščiavimas 40 – 60%, viduriavimas net iki 46%. Pirminiai simptomai, vėmimas bei dirglumas, pirmiausiai signalizuoja apie kitas patologijas, tokias kaip gastroenteritas ar mezenterinis limfadenitas ir ūminio apendicito diagnozė nustatoma vėlai (2). Mūsų atliktame tyrime komplikuotas ūminis apendicitas pasireiškė dažniau nei nekomplikuotas apendicitas taip pat tik 0 – 5 metų amžiaus vaikų grupėje.

Esant ūminiam apendicitui, kaip ir bet kokiai kitai infekcijai, kraujyje didėja uždegiminiai rodikliai, tokie kaip leukocitų ir neutrofilų skaičius, c-reaktyvusis baltymas (24). Šių rodiklių diagnostinė reikšmė ūminiam apendicitui yra plačiai analizuojama literatūroje. Charity C. Glass ir Shawn J. Rangel 2016 metais publikuotoje vaikų ūminio apendicito diagnostikos apžvalgoje rasta, kad tarp skirtingų studijų absoliutaus leukocitų skaičiaus tyrimo jautrumas ūminio apendicito diagnostikoje varijuoja nuo 70% iki 80%, o tyrimo specifiškumas nuo 60% iki 68% (25). Absoliutaus neutrofilų skaičiaus tyrimas pasižymi panašiu jautrumu bei specifiškumu, atitinkamai, nuo 59% iki 97% ir nuo 51% iki 90%. C-reaktyvaus baltymo jautrumo ir specifiškumo variacijos tarp atliktų studijų yra dar didesnės, jautrumas aprašomas 58% ir 93% ribose, specifiškumas 28% – 82% (25). Nors uždegiminiai rodikliai gali padėti nustatyti apendicito diagnozę, tačiau tai nėra patognominiai ligos požymiai, be to, iki 20% vaikų gali sirgti ūminiu apendicitu be neutrofilinės leukocitozės, o c-reaktyvusis baltymas daugiau pradeda didėti jau esant kirmėlinės ataugos perforacijai, t. y. vėlyvai apendicito stadijai (26,27). Kadangi šie tyrimai nepasižymi didele prognostine reikšme, instrumentiniai tyrimai

naudojami kaip papildoma diagnostinė priemonė nustatyti ūminį apendicitą. Dažniausiai naudojamas pilvo ultragarsas, nes jis yra pigesnis nei pilvo kompiuterinė tomografija ar magnetinio rezonanso tomografija, taip pat pilvo UG nereikalauja sedacijos, neskleidžia jonizuojančios spinduliuotės, nenaudojamos kontrastinės medžiagos (25). Remiantis naujausia literatūra, geriausias ūminio apendicito diagnostinis kriterijus yra KA diametras > 6 mm (28). Tačiau Tristan Reddan kartu su savo bendraautoriais atliko 3 metų retrospektyvią duomenų analizę ir nustatė, kad ūminio apendicito diagnostikoje naudojama KA diametro 6 mm riba daliai atvejų visgi lemia klaidingai teigiamą diagnozę, kuomet laparoskopijos metu KA stebima be pakitimų. Dėl to autoriai pabrėžia antinių ultragarsinių pokyčių svarbą: laisvo skysčio pilvo ar dubens ertmėje buvimą, KA kaprolito buvimą, aplinkinės taukinės uždegiminius pokyčius, išsiplėtusias žarnų kilpas (29). Be to, apendiksas ne visada gali būti vizualizuojamas UG metu, tyrimo kokybė priklauso nuo radiologo patirties (28). Mūsų biomedicininiam tyrimui surinktais UG duomenimis mažiausias išmatuotas KA diametras buvo 7 mm, vidutinis diametras siekė 9.9 mm (SD ± 2.322), laisvas skystis UG metu stebėtas 39% atvejams. Tyrimo metu klaidingai teigiamų ūminio apendicitų diagnozių nestebėta.

Ūminio apendicito gydymas vis dar išlieka kontraversiškas. Nors laparoskopinė apendektomija laikoma auksiniu standartu, kai kurie gydymo centrai nekomplikuotą ūminį apendicitą renkasi gydyti konservatyviai (30–32). Peter C. Minneci kartu su bendraautoriais atliko multi-centrinę studiją, kurioje lygino skirtingas gydymo metodikas. Į tyrimą įtraukė 1068 pacientus, iš kurių 370 rinkosi konservatyvų gydymą. Vienerių metų laikotarpyje 67,1% pacientų operacijos taip ir neprireikė (31). Emily Decker ir bendraautoriai atliko sisteminę apžvalgą palyginti konservatyvų ir chirurginį nekomplikuoto ūminio apendicito gydymo metodus. Abejose pacientų grupėse gauti panašūs rezultatai, konservatyvaus gydymo sėkmės dažnis siekė 80% 30 dienų laikotarpyje ir 68% vienerių metų laikotarpyje, tuo tarpu komplikacijų dažnis po laparoskopijos – 10% (32). Mūsų gydymo centre visgi renkamasi visus ūminio apendicito atvejus operuoti, atlikti laparoskopinę apendektomiją, konservatyviai gydomi tik lėtiniai apendicitai (susiformavę infiltratai). Tobulėjant operaciniam gydymui, atvirą apendektomiją pakeitė laparoskopinė, o paskutiniu metu atsiranda ir dar naujesnių bei mažiau invazyvių laparoskopijos variacijų, pavyzdžiui vieno porto transumbilikalinė apendektomija (TULA). Naujausių tyrimų duomenimis, TULA pasižymi geresniu kosmetiniu rezultatu, trumpesne operacijos bei hospitalizacijos trukme, mažesniu pooperacinių komplikacijų skaičiumi, mažesniu pooperaciniu skausmu (33–35). Šiame biomediciniame tyrime 33% procentams pacientų atlikta TULA, kurios vidutinė trukmė buvo tumpesnė nei standartinė trijų portų laparoskopinė apendektomija, hospitalizacijos trukmė taip pat

abskaičiuota statistiškai reikšmingai trumpesnė po TULA metodo. Taip pat mūsų tyrimo duomenimis rastas ryšys tarp TULA ir mažesnio pacientų KMI, kas nurodo, jog TULA galima atlikti tik esant mažesnei paciento pilvo apimčiai.

6.2. Pooperacinės komplikacijos ir galimi rizikos veiksniai

Atliktas tyrimas parodė, kad Vilniaus tretinio lygio ligoninėje komplikacijų skaičius po laparoskopinių apendektomijų vaikams siekia 6,8%. Tai atitinka literatūroje pateiktus užsienio statistinius duomenimis, kur šis dažnis varijuoja nuo 5% iki 25% **(9 lentelė)**. Tyrimo rezultatai džiugina, kadangi esame tarp mažiausiai komplikacijų turinčių centrų.

9 lentelė. *Pooperacinių komplikacijų po laparoskopinių apendektomijų vaikams variacija literatūroje.*

Autoriai	**Publikacijos metai**	**Pacientų skaičius**	**Pooperacinių komplikacijų dažnis**
Jan F. Svensson et al. (36)	2015	1010	12,3%
Jong Wan Kim et al. (37)	2017	1753	10%
Liu Y et al. (4)	2017	190	13%
M. D. Bolmers et al. (38)	2018	319	11,9%
Max Knaapen et al. (39)	2020	131	25%
Mohammad Gharieb Khirallah et al. (40)	2021	75	25.3%
Fourie N et al. (41)	2022	51	25.5%
Edoardo Bindi et al. (42)	2023	181	4,4%
Rebecca John et al. (34)	2023	1154	<5.0%
Shuo-Lun Lai et al. (43)	2024	1343	9,68%

Dauguma studijų analizuoja dažniausiai pasitaikančias komplikacijas (intraabdominalinius pūlinius, chirurginės žaizdos infekcijas, žarnų nepraeinamumą). Max Knaapen drauge su bendraautoriais savo tyrime registravo bet kokias kilusias postoperacines komplikacijas, kurios rekalavo papildomo gydymo: žaizdos infekcijos, pilvo ertmės pūliniai, pilvo ertmės apendikuliariniai infiltratai, žarnyno nepraeinamumas, fistulės, nežinomos kilmės pilvo skausmas, ūminis respiracinis distreso sindromas, šokas. Jie savo tyrime fiksavo 25% pooperacinių komplikacijų dažnį (39). Šiame tiriamajame darbe skaičiuodami pooperacinių

komplikacijų dažnį taip pat siekėme registruoti ne tik dažniausias, bet visas kilusias komplikacijas, dėl to buvo nuspręsta su tėvais susisiekti telefonu norint nepraleisti net menkiausių žaizdų infekcijų, dėl kurių tėvai galimai nesikreiptų į gydymo įstaigą. Per visą prospektyvinio tyrimo dalį mūsų centre nebuvo nei vienos žarnyno nepraeinamumo komplikacijos, nors tai literatūroje laikoma dažna komplikacija po laparoskopinės apendektomijos. Daugiausiai registravome chirurginių žaizdų infekcijų. Postoperacinių komplikacijų dažnis mūsų klinikiniame tyrime komplikuotų ūminių apendicitų grupėje siekia 11,11%. Literatūros duomenimis šis skaičius gali siekti iki 35.5% (44).

Vieningos nuomonės dėl rizikos veiksnių literatūroje nėra. Mohammad Gharieb Khirallah ir bendraautoriai (2021) nustatė, kad absoliutus leukocitų skaičius > 14,000 c/mm^3, ilgiau nei 2 dienas trunkantys ligos simptomai, KMI > 23, ilgesnė operacijos trukmė turi didesnę įtaką formuotis pooperacinėms komplikacijoms. Autoriai savo tyrime nestebėjo skirtumo komplikacijų išsivystymui tarp operacijos metu pilvo ertmėje esančio laisvo skysčio siurbimo ir siurbimo kartu su pilvo ertmės plovimu, taip pat nustatė, kad ir dreno įvedimas po oeracijos neturi reikšmės komplikacijų išsivystymui (40). Francisco Schlottmann ir bendraautoriai (2017) identifikavo, kad išsivystyti komplikacijoms po laparoskopinės apendektomijos didesnė rizika yra nutukusiems pacientams (KMI > 30), pacientams, kurių absoliutus leukocitų skaičius viršija 20,000 c/mm^3, randama KA perforacija ar apendektomija trunka > 90 min (5). Keletas studijų pilvo skausmo trukmę laiko esminiu ligos sunkumo rodikliu (37,45,46). Tuo tarpu Guy ir Wysocki (2018) savo tyrime nerado stiprios koreliacijos nei su vienu rizikos veiksniu (47). Skirtingą komplikacijų rizikos veiksnių identifikavimą gali lemti skirtingi statistiniai skaičiavimo metodai, naudojami straipsniuose, skirtingos imtys, skirtingos duomenų rinkimo metodikos, skirtingi regionai. Mūsų klinikiniame tyrime rastas statistiškai reikšmingas skirtumas tarp atvejų su kompikacijomis ir atvejų be komplikcijų analizuojant pacientų kūno masės indeksą (KMI), simptomų trukmę, absoliutų leukocitų skaičių, kirmėlinės ataugos diametrą, ultragarso tyrimo metu stebėtą laisvą skysčią, operacijos trukmę. Tačiau stiprios koreliacijos nūsų tyrimo duomenimis nenustatyta nei su vienu rizikos veiksniu.

7. IŠVADOS IR PASIŪLYMAI

Ūminis apendicitas dažniausia vaikų chirurginė pilvo skausmo priežastis, dėl to tai vis dar išlieka labai aktuali tema siekiant gerinti esamus gydymo metodus bei palikti kuo įmanoma mažesnį pooperacinį randą. Surinkus duomenis vaikų, kuriems dėl ūminio apendicito atlikta

laparoskopinė apendektomija Vilniaus Universiteto Santaros Klinikų vaikų chirurgijos skyriuje, gauti tokie rezultatai:

1. Atvejų, kuomet po laparoskopinės apendektomijos nepasireiškė nei viena komplikacija, tyrimo metu buvo 137 iš 147 (93,2%).
2. Tyrimo laikotarpiu iš viso registruota 10 (6,8%) komplikacijų po laparoskopinės apendektomijos. Komplikacijų skaičius Vilniaus Universiteto Santaros Klinikų vaikų chirurgijos skyriuje atitinka literatūroje pateiktus užsienio statistinius duomenimis. Svarbu paminėti, kad esame tarp mažiausiai kompikacijų turinčių ligoninių.
3. Siekiant identifikuoti galimus rizikos veiksnius komplikacijoms po laparoskopinės aendektomijos vaikams rastas statistiškai reikšmingas skirtumas tarp atvejų su kompikacijomis ir atvejų be komplikcijų analizuojant simptomų trukmę, absoliutų leukocitų skaičių, kirmėlinės ataugos diametrą, ultragarso tyrimo metu stebėtą laisvą skysčią, operacijos trukmę ir pacientų kūno masės indeksą.

Norint mažinti komplikacijų skaičių ateityje, reikia šviesti visuomenę apie galimus ūminio apendicito simptomus bei gerinti diagnostikos galimybes anksti diagnozuoti ligą ir skatinti gydytojus tobulinti laparoskopijos techniką įvairiuose mokymuose, kad reali operacija truktų kuo trumpiau.

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Associated intraabdominal malformations of right-sided congenital diaphragmatic hernia: A rare anomaly and review

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ABSTRACT

There is scarce literature on associated anomalies of right-sided congenital diaphragmatic hernias (CDH). The purpose of this study was to expand the presentation of a unique clinical experience by a literature review. Only six articles of a right-sided CDH linked to non-cardiac anomalies with complicated diagnostic and treatment scenarios were found related to ours. To the best of our knowledge, it is the first presented case of a right-sided CDH with multiple intestinal atresias and an intrathoracic right kidney. This case alerts physicians to take all examination details into account to avoid delaying CDH diagnosis. Most importantly, it gives valuable insight into possible associated anomalies of right-sided congenital diaphragmatic hernias and may benefit future embryological or genetic studies.

1. Introduction

Congenital diaphragmatic hernia (CDH) is described as a defect in the diaphragm that allows abdominal organs to herniate into the thoracic cavity. CDH is a rare anomaly with an occurrence rate ranging from one to five in 10,000 live births [1]. According to existing literature, right-sided diaphragmatic hernias are less common (15%) than left-sided (85%) and carry a higher risk of mortality and morbidity [2]. In 40–50% of cases, CDH is associated with other congenital anomalies such as central nervous system defects, cardiac and genitourinary pathologies. However, associated non-cardiac congenital malformations of right-sided CDH are underrepresented in literature. Its coexistence with intestinal atresia is extremely rare, with a single case of a right-sided CDH and duodenal atresia reported in literature [3–5]. Coexistence with intrathoracic kidney was reported but the combination of both duodenal and jejunal atresias, with intrathoracic renal ectopia is unique. The aim of this study was to analyse complicated diagnostic and therapeutic management and to conduct a literature review.

2. Methods

Informed consent from patient's parents was obtained. Demographic characteristics, clinical history, imaging data and management were assessed from medical documents and electronic data files. The literature search was made using the electronic National Institute of Health database PubMed.gov. For the search terms "Right-sided diaphragmatic hernia AND duodenal atresia AND jejunal atresia AND intrathoracic renal ectopia" were used, however, no results were found. Further search was performed in order to select

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any linked papers using search terms "Right-sided diaphragmatic hernia AND congenital anomaly". From 273 detected articles, six papers relevant to our case were selected. Experience of other centers presented in Table 1 was compared to our clinical experience.

3. Case description

A female neonate weighing 1600 g with Apgar scores of eight at the first and the fifth minutes was born through a standard vaginal delivery at 30 weeks of gestation and referred to our tertiary level neonatal intensive care unit (NICU). Her prenatal ultrasound showed signs of duodenal atresia at the 26th gestational week with no other signs of congenital malformations. The baby presented with signs of proximal bowel obstruction and respiratory distress, due to which continuous positive airway pressure (CPAP) was initiated. An abdominal ultrasound revealed an aperistaltic, dilated duodenum, filled with liquid content, and distally empty intestinal loops, consistent with duodenal atresia findings. A renal ultrasound identified a single left kidney with suspected right kidney agenesis. Chest X-ray showed an unclear opacification of lower segments of the right lung, reduced lung aeration, and distended stomach (Fig. 1). No pleural effusion or pathological changes in diaphragm integrity were observed by ultrasound of pleura and lungs or sus-

Table 1
Previously reported cases of right-sided CDH and associated anomalies.

Study (year of publication)	Associated anomaly	Existence of cardiac anomaly	Birth weight, g	Time of CDH diagnosis (prenatally/postnatally)	Outcome
Castle et al. (2011)	VACTERL	Yes	3010	Postnatally	Survived
Chen et al. (2013)	VACTERL	Yes	2830	Postnatally	Survived
Olenik et al. (2014)	Hepatopulmonary fusion	No	2885	Prenatally	Survived
Juricic et al. (2016)	Intrathoracic kidney	No	3905	Prenatally	Survived
Takezoe et al. (2017)	Intrathoracic kidney; hepatopulmonary fusion	No	2780	Prenatally	Survived
Almaramhy et al. (2018)	Hepatopulmonary fusion	No	Not presented	Postnatally	Died on the 3rd postoperative day

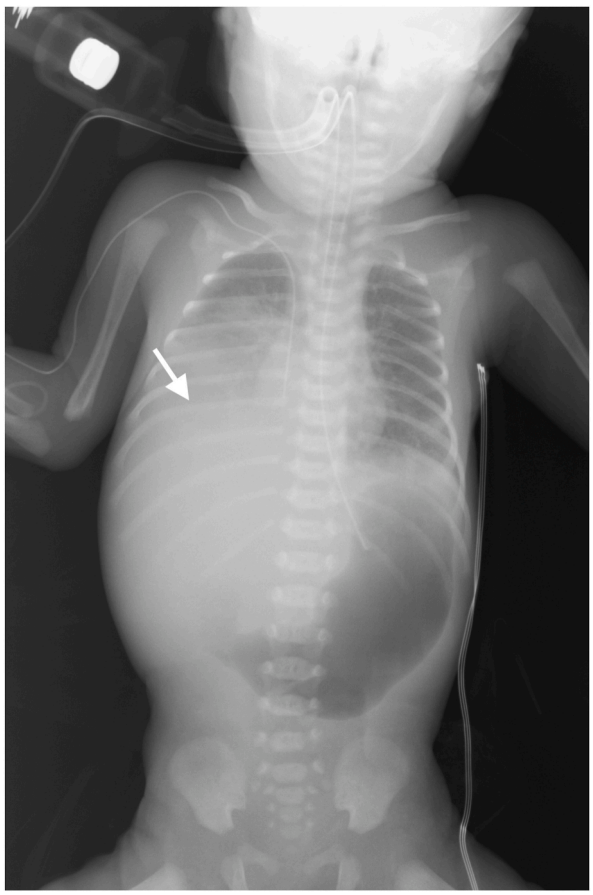

Fig. 1. 2nd day chest x-ray. Undefined opacification of lower right lung segments and reduced lung aeration (white arrow).

pected on chest x-rays. Right lung atelectasis was believed to be the cause of the impaired lung function, and the baby was subsequently intubated.

A laparotomy was done for duodenal atresia repair. During the operation, a segment of jejunum was observed in adhesions. Having dissected it, a 3cm jejunal atretic segment with recanalization on its medial side was observed (Fig. 2). Duodenal atresia was repaired by a Kimura duodenoduodenostomy, while the atretic nonfunctioning jejunal segment was excised, and a feeding tube was easily passed through the recanalized jejunum. The surgeons did not identify a diaphragmatic hernia during the procedure since the liver was lying in its proper position covering the diaphragmatic defect.

Due to deteriorating respiratory distress postoperatively, an ultrasound of the pleura and lungs was carried out. It revealed an additional pulmonary mass with accessory arterial supply from the aorta, implying a possible pulmonary sequestration. In addition, the ultrasound showed an abnormally high positioned right kidney. However, subsequent ultrasonographic examination alongside renal ectopia suggested intrathoracic anomalous liver tissue and likely heterogeneity of the right diaphragm (Fig. 3). It was the first time the newborn was suspected of having a diaphragmatic hernia. A chest computed tomography (CT) (Fig. 4) was obtained to differentiate between a pulmonary sequestration and possible hepatopulmonary fusion, however it did not clarify the final diagnosis. Subsequently, on the fourth postoperative day, a diagnostic right thoracoscopy (Fig. 5) was performed, and a 4cm right-sided diaphragmatic hernia with herniation of the right kidney and upper liver edge was finally confirmed. On account of the high kidney position, conversion to laparotomy was chosen, and, having returned abdominal organs to the abdominal cavity, the diaphragmatic hernia was repaired with single sutures. The second postoperative period was uncomplicated.

4. Discussion

To the best of our knowledge, there has only been one case of a right-sided CDH associated with duodenal atresia reported in literature [4]. Our presented case is the first described right-sided CDH with multiple intestinal atresias and a right intrathoracic kidney. We were able to find very few clinical cases of various non-cardiac associated anomalies of a right-sided CDH (Table 1).

Congenital diaphragmatic hernia is a rare clinical finding, and its etiology is not fully understood. It has been proposed that the development of CDH might be influenced by nutritional deficiencies, environmental exposure, and genetic factors [6]. One of the etiological theories suggests that low vitamin A intake might be the driving mechanism of abnormal diaphragm embryogenesis through impaired retinoid signaling. In 2021, Rocke et al. published a study in which, for the first time, a correlation between inadequate maternal vitamin A intake and susceptibility to teratogen-induced CDH was demonstrated in a rat model [7]. According to the latest literature, about 30% of CDH cases in neonates are caused by genetic factors, such as mutations of the WT1 transcription factor (WT1), chick ovalbumin upstream promoter transcription factor II (COUP-TFII), GLI-Kruppel family member 2 (GLI2), and others [8]. CDH has been linked with autosomal recessive, autosomal dominant, and X-linked patterns of inheritance. Nevertheless, etiology remains unspecified in more than 70% of all CDH cases [9].

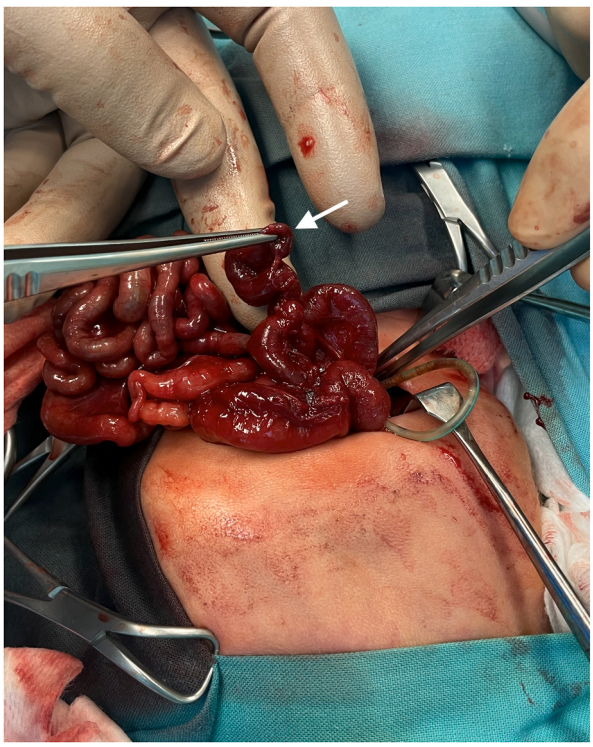

Fig. 2. First surgery. A recognized 3cm jejunal atretic segment (white arrow) during the first surgery.

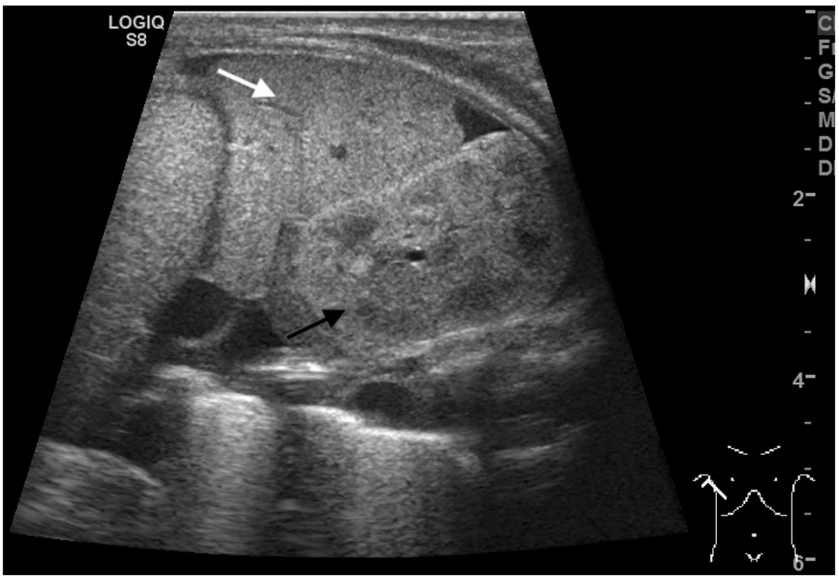

Fig. 3. Post-operative thoracic ultrasonography. Intrathoracic renal ectopia (black arrow) and possible intrathoracic liver tissue (white arrow).

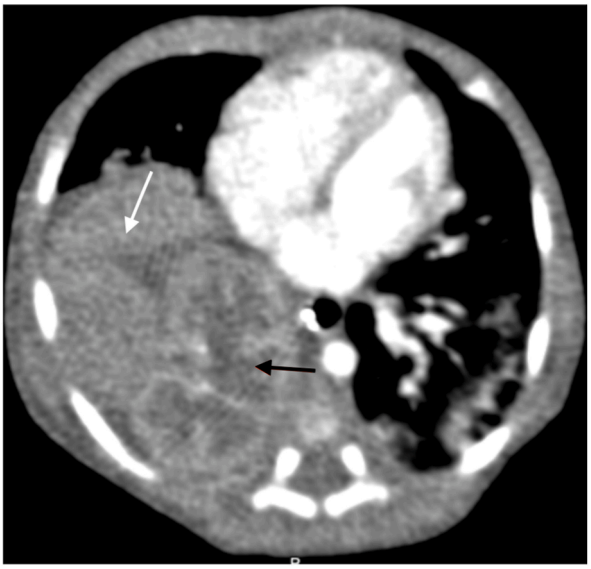

Fig. 4. Post-operative chest CT. Intrathoracic renal ectopia (black arrow) and possible intrathoracic liver tissue (white arrow).

Furthermore, some authors have suggested that right and left-sided CDH may be ethiopathogenetically different and that the type of associated nondiaphragmatic malformations may be linked to the side of the diaphragmatic defect [10,11]. R. Grizjel has disputed this theory, however there is still a significant lack of literature regarding concomitant malformations of right-sided CDH in order to make complete conclusions [12]. Reporting on and analyzing associated congenital malformations may help decipher the embryonic development of CDH and conclude if right and left CDH are two distinct entities.

There is varied literature on antenatal diagnosis of the right-sided CDH. According to Jani et al., right-sided CDH is challenging to diagnose prenatally by ultrasound in cases where the liver is the only organ that has herniated because of its similar echogenicity to that of lungs [5]. Although, in their study Hedrick et al. succeeded in diagnosing right-sided CDH prenatally in 81,5% of all cases, current literature implies that in contrast to right-sided, left-sided congenital diaphragmatic hernias are easier to diagnose antenatally because they may appear as heterogeneous masses in the thoracic cavity [6,13,14].

If a diaphragmatic hernia remains unidentified before birth, there are certain key points to follow in order to diagnose it postnatally. CDH might cause diminished breath sounds on the ipsilateral side of the hernia, a shift of heart sounds contralaterally, and a scaphoid abdomen. Visible bowel gas above the diaphragm and mediastinal shift on chest x-ray confirm the presence of diaphragmatic hernia [15–18]. Sometimes a right-sided CDH can be mistaken for pneumonia or lung atelectasis on a chest X-ray as reported in the case described by Duan et al. and as was our experience [19]. It is important to note that in the presence of an unidentified in-

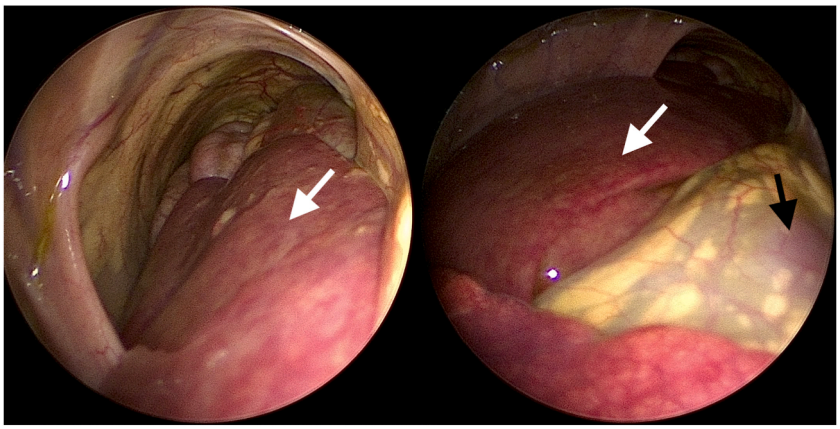

Fig. 5. Diagnostic thoracoscopy. Right-sided diaphragmatic hernia with herniation of the right kidney (black arrow) and upper liver edge (white arrow).

trathoracic mass and the absence of the kidney ipsilaterally, CDH should always be suspected [20,21]. The difficult diagnostic process that we faced adds up to existing literature stating that right-sided CDH often requires complex examination [6,14].

In our clinical case, duodenal atresia was diagnosed on the 26th gestational week using transabdominal ultrasound, whereas CDH was not suspected before birth. In the case described by Castle et al., duodenal atresia was also diagnosed prenatally, while CDH was confirmed after the first neonatal chest X-ray. Early postnatal CDH diagnosis was aided by the fact that a dilated duodenum could be seen in the thoracic cavity as opposed to our clinical case experience [4]. In our presented tricky clinical scenario, the original chest x-ray did not raise any suspicion of herniated viscera. Retrospectively, we believe that a few facts complicated the diagnosis of CDH in this clinical case. Firstly, the liver was covering the diaphragmatic defect, so the abdominal organs could not pass through it into the chest. Most likely, the right kidney had already been herniated into the thoracic cavity when the first chest x-ray was performed, however as there were no clear margins of the opacity in the right thorax, a solid mass was not considered. Owing to the little amount of herniated content and low intrabdominal pressure caused by duodenal atresia, lung development of the neonate was not strongly disrupted, leading to atypical CDH symptoms. After managing duodenal atresia, the bowel began to function, and, under increased intraabdominal pressure, the upper liver edge protruded into the thoracic cavity, causing respiratory distress and subsequent right-sided CDH diagnosis.

5. Conclusion

The coexistence of a right-sided congenital diaphragmatic hernia and multiple intestinal atresias, and intrathoracic renal ectopia in the same individual is an exceptional clinical finding. Diagnosing this type of hernia might be challenging. All examination details must be taken into account and considered thoroughly in order to avoid complications that may be fatal. In the absence of a right kidney and ipsilateral lung opacity, right-sided CDH should be considered and operative management should be planned accordingly in order to avoid possible complications. This rare case can provide further insight into the pathophysiology and associated anomalies of right-sided congenital diaphragmatic hernias and benefit future embryology studies.

Patient consent

Informed consent from patient's parents was obtained.

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Authorship

All authors attest that they meet the current ICMJE criteria for Authorship.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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COVID-19 Case Report

Aortic thrombosis after DVT and PE in a young COVID-19 patient

Tomas Baltrūnas,[1,2] Austėja Račytė,[1] Gabija Pikturnaitė,[1] Arminas Skrebūnas,[1,2] and Birutė Vaišnytė[1,2]

Abstract: A rare case of aortic thrombosis in a young COVID-19 positive patient is presented in this case report. Arterial thrombosis developed despite the administration of anticoagulants for treating DVT and PE. The patient underwent axillobifemoral bypass surgery. Limited surgical surveillance, administered steroids and critical health status resulted in wound site infection and consequent graft removal. Aortic endarterectomy and autovenous-patch plasty were performed after the patient's condition improved. Etiopathogenesis of arterial events in the setting of COVID-19 is not entirely understood. It has been suggested that SARS-CoV-2 infection strongly affects vascular endothelial glycocalyx (VEGLX), causes systemic inflammation - reactive microvascular endotheliosis (SIRME), and consequently results in arterial thrombosis.

Coronavirus disease 2019 (COVID-19) can result in various complications outside the respiratory tract including renal failure, neurological symptoms, septic shock, myocardial injury as well as coagulopathies. Prothrombotic condition in severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infected patients can lead mostly to venous thromboembolism (VTE), deep vein thrombosis (DVT), and less frequently to arterial thrombotic events.[1–3] Even though arterial thrombosis in COVID-19 patients is less common than venous thrombotic events, recently published studies imply that the rate of arterial thrombosis in such a clinical setting is growing.[1] Therefore, it is critically important to understand the pathological mechanisms of excessive arterial blood clotting which can lead to acute limb ischemia, myocardial infarction, and stroke.[4] Once the pathogenesis is fully understood, it will be easier to prevent and manage arterial thrombosis. It is important to increase awareness to succeed with early diagnosis by differentiating vasospasm, hypoxia, and acidosis caused by COVID-19 from those caused by arterial thrombotic events. A case of a young patient with thrombosis of the infrarenal aorta and bilateral occlusion of iliac arteries in the setting of COVID-19 is presented. Moreover, the patient has developed pulmonary embolism (PE) despite being on prophylactic dose of anticoagulants.

CASE REPORT

On December 15, 2020, a 51-year-old man was presented to an emergency department with chest pain and hypertensive crisis (arterial blood pressure, 220/110 mmHg) which was corrected with peroral drugs (ACE inhibitors). The patient's vital signs during admission were as follows: heart rate, 81 beats/min; temperature, 36,9°C; oxygen saturation, 95% with supplemental oxygen flow of 3 liters/min. The patient underwent a chest computed tomography angiography (CTA) scan with no signs of PE. However, the CTA scan showed bilateral pneumonia and subsequently, patient was tested positive for COVID-19. According to the latest local protocol, amoxicillin with clavulanic acid

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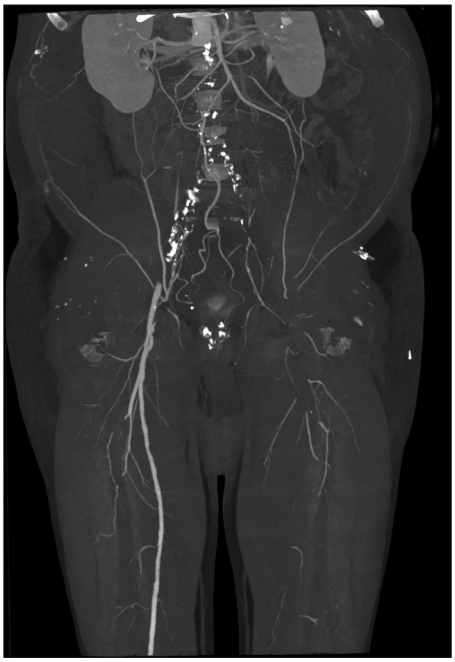

Fig. 1. CTA reconstruction. Aortoiliac occlusion.

was administered as well as dexamethasone, low-molecular-weight heparin in prophylactic dosage, and oxygen. The patient started complaining of worsening pain and weakness in the left lower limb on consecutive days. On December 17, because of high D-dimers (22145 ng/mL), venous duplex ultrasound was performed and no venous pathology was found. Leg pain was getting worse and the left femoral artery pulse could not be palpated. Due to deteriorating health status, a chest and lower extremities CTA was carried out on December 23. It showed bilateral viral pneumonia with partial resorption, as well as PE in the right middle lobes of lateral and medial segments. Due to occurred PE low-molecular-weight heparin dose was increased from prophylactic to therapeutic. CTA also revealed thrombosis of infrarenal aorta, bilateral common iliac arteries, and left external iliac artery. The proximal sections of left internal iliac and mesenteric inferior arteries were occluded as well (Fig. 1). Surgical revascularization was postponed because of the patient's severe condition and borderline saturation level which was only about 80% with maximum oxygen flow due to COVID-19 and PE. At that point in time limb ischemia was not critical and according to the local hospital's protocol of COVID-19 patient management, intubation must be avoided as long as it is possible. The patient's leg ischemia deteriorated the following days and the surgery was considered again. On December 28, the patient was stable enough to place the extra-anatomic axillo-bifemoral bypass. Endovascular treatment was rejected because of the unknown etiology of arterial thrombosis in the setting of COVID-19. Axillo-bifemoral bypass was chosen instead of aortobifemoral to carry out a less invasive procedure. However, on the 3rd post-operative day wound healing appeared to be compromised. Vascular graft infection was confirmed by ultrasound scan on the 5th postoperative day. Several risk factors might have contributed to the graft infection: ongoing pneumonia, prolonged preoperative hospitalization, administration of corticosteroid, obesity, limited access treatment in the COVID-19 unit. As soon as the patient was fully recovered from COVID-19, he was transferred to the Vascular Surgery unit. On January 8, the infected axillo-bifemoral shunt was removed. Additionally, an open endarterectomy of infrarenal aorta, right common iliac, and left external iliac arteries as well as remote endarterectomy in the left common iliac artery were performed. The left great saphenous vein was used for autovenous-patch plasty of the right common iliac, left external iliac, and bilateral common femoral arteries. The blood flow was restored to the patient's legs successfully: left popliteal pulse, as well as pulse in the left foot, were present. There were no complications during postoperative period, hence the patient was discharged from the hospital on the 25 of January.

DISCUSSION

Lately, a growing number of studies and case reports on coagulopathies associated with COVID-19 infection can be found. Despite the increasing number of thrombotic events in COVID-19 patients, the pathogenesis of hypercoagulability in this particular clinical setting is still poorly known.[5] Therefore, many theories have emerged to explain this problem. It has been suggested that all three components of Virchow's triad can be affected by the novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).[6] Changes of prothrombotic factors, such as factor VIII, fibrinogen, neutrophil extracellular traps can be observed in patients critically ill with COVID-19 and they are reported to promote a hypercoagulable state.[7] Numerous experts have postulated that endothelial dysfunction plays a central role in the pathogenesis of clot formation in severely ill COVID-19 patients.[8–11] Some studies have reported that the alternative complement pathway is activated by SARS-CoV-2 spike protein,

which eventually results in the elevation of markers of complement activation and endothelial injury.[12] Moreover, endothelial dysfunction can be exacerbated by viral or bacterial inflammation because under such circumstances tissue factor (TF) production is elevated, as well as granulocytes, monocytes, and several cytokines including interleukin-6 (IL-6), tumor necrosis factor-alpha (TNFα).[13] According to Minako Yamaoka-Tojo, the underlying cause of endothelial dysfunction during COVID-19 infection is the damage of vascular endothelial glycocalyx (VEGLX). It is a gel-like layer covering the inside of blood vessels and functioning as a barrier for vascular endothelial cells as well as controlling intracellular signals.[11,14] It has been well documented that hypertension, diabetes, heart failure, ischemic heart disease, kidney diseases, atherosclerosis, stroke, sepsis, multiple organ failure as well as obesity, smoking, and old age can lead to impaired VEGLX. On the other hand, VEGLX can also be strongly affected by SARS-CoV-2, which invades vascular endothelium and causes systemic inflammatory changes in endothelial cells as well as induces the release of inflammatory cytokines and leakage of plasma components resulting in VEGLX destruction and shedding. These pathological processes can be defined by systemic inflammation reactive microvascular endotheliosis (SIRME). It has been suggested that SARS-CoV-2 can better penetrate the endothelial cells with already impaired VEGLX on account of underlying diseases. Therefore, lethal conditions, for instance, acute respiratory distress syndrome (ARDS) or disseminated intravascular coagulation (DIC) have a higher incidence rate among COVID-19 patients that have at least one previously diagnosed chronic disease. As the fragmented VEGLX level in patient blood correlates with COVID-2019 severity, it is believed to be beneficial as a prognostic indicator.[10] However, in this clinical case, the amount of VEGLX was not tested. Risk management and treatment of thrombotic complications due to COVID-19 are challenging owing to the lack of high evidence data. According to the International Society on Thrombosis and Haemostasis, all hospitalized SARS-CoV-2 infected patients should get prophylactic anticoagulation therapy,[15] particularly those with risk factors such as smoking, physical inactivity, hypertension, diabetes, obesity, cardiovascular diseases, male gender, and older age.[16] However, it is being more commonly reported in existing literature as well as in our clinical experience that despite administration of thromboprophylaxis thrombotic events may still occur.[4,17,18] Extensive clinical trials are needed to clarify the best ways of preventing and managing thrombotic complications during COVID-19.

CONCLUSIONS

Arterial thrombosis in the clinical setting of COVID-19 appears less commonly than venous thrombotic events. However, it is crucially important to maintain a high index of suspicion on arterial manifestations. It can be challenging to diagnose it early because vasospasm, hypoxia as well as acidosis can be understood as symptoms of COVID-19, while they can appear due to arterial thrombosis. Also, delayed diagnosis can lead to severe complications and result in increased mortality and morbidity rate. Overall, COVID-19 has given various insights on mechanisms of arterial thrombosis which could potentially be used in clinical practice outside the field of COVID-19.

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Išeminių audinių perfuzijos pokyčiai atkuriant kraujotaką tiesiogiai pagal angiosomą ir netiesiogiai

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Santrauka. *Įvadas.* Vis populiarėja galūnės kraujotakos atkūrimas pagal angiosomas, esant kritinei galūnės išemijai, t. y. revaskuliarizuojama būtent ta kraujagyslė, kuri maitina pažeistą plotą. Tačiau revaskuliarizacija atsižvelgiant į angiosomas nėra laikoma kritinės galūnių išemijos gydymo standartu, nes mokslinėje literatūroje trūksta įrodymų, pagrindžiančių šio gydymo metodo pranašumus. Pristatomo tyrimo tikslas – palyginti audinių oksigenacijos pokyčius išeminėje zonoje, endovaskuliniu būdu atkūrus kraujotaką tiesiogiai pagal angiosomą ir netiesiogiai. *Metodai.* Tai perspektyvusis stebimasis tyrimas. Į tyrimą įtraukti pacientai, kuriems diagnozuota kritinė galūnės išemija, esant gangrenai dėl užakusių blauzdos arterijų. Pacientams taikyta endovaskulinė revaskuliarizacija. Procedūros metu oksigenacijos pokyčiai stebėti naudojant artimųjų infraraudonųjų spindulių spektroskopiją. Gauti rezultatai lyginti pacientų, kuriems taikyta tiesioginė ir netiesioginė revaskuliarizacija, grupėse. *Rezultatai.* Tiriamąją imtį sudarė 30 pacientų, sergančių kritine galūnių išemija (5 Rutherfordo kategorija). Visiems pacientams nustatyta blauzdos arterijų okliuzija, kai reikia atkurti kraujotaką. Tyrimo metu 15 pacientų (50 %) kraujotaka buvo atkurta pagal angiosomą, tokiai pat daliai pacientų (50 %) – ne pagal angiosomą. Visiems tiriamiesiems procedūros metu matuoti oksigenacijos pokyčiai išeminėje zonoje. Didesnis oksigenacijos pokytis pastebėtas pacientų, kuriems atlikta revaskuliarizacija pagal angiosomą, grupėje (atitinkamai 29 proc. ir 23 proc.), bet statistiškai reikšmingo oksigenacijos skirtumo tarp grupių nenustatyta (nepriklausomos grupės t testas, p = 0,544). *Išvados.* Klinikinio tyrimo metu audinių oksigenacijos pokytis atkuriant kraujotaką pagal angiosomą mažai skyrėsi nuo audinių oksigenacijos pokyčio atkuriant kraujotaką ne pagal angiosomą. Skirtumas nebuvo statistiškai reikšmingas.

Reikšminiai žodžiai: kritinė galūnių išemija, angiosoma, artimųjų infraraudonųjų spindulių spektroskopija, endovaskulinė revaskuliarizacija.

Tissue Perfusion Changes after Direct and Indirect Angiosome Revascularization in Critical Limb Ischemia

Abstract. *Background.* Blood flow restore in critical limb ischemia according to angiosomes is becoming very popular. This method allows to restore blood flow precisely to the artery supplying the ischemic zone, based on the angiosome concept. However, angiosome revascularization is not a gold standard because of the lack of evidence supporting this approach. The aim of this study was to compare tissue oxygenation changes in ischemic zone during endovascular revascularization procedure either following angiosome concept or performing indirect revascularization. *Methods.* A prospective observational study was performed. Patients with critical limb ischemia and tissue loss due to chronic total occlusion of below the knee arteries were included. Endovascular revascularization was performed in all cases. Tissue oxygen saturation was observed intraoperatively using near-infrared spectroscopy. Tissue oxygenation changes near the ischemic wound were compared between direct and indirect revascularization groups. *Results.* This clinical trial included 30 patients with critical limb ischemia (Rutherford 5) and occluded below the knee arteries intended to treat. In 15 patients the procedure was performed according to angiosome, while the other half underwent indirect revascularization. Tissue oxygenation near the wound was monitored during the intervention. Greater oxygen saturation increase was observed in the group with direct revascularization (29% and 23% accordingly), however the difference between groups was not statistically significant (t-test for independent group, p = 0,544). *Conclusions.* The increase in tissue oxygen saturation differed very slightly in direct and indirect revascularization groups and the difference was statistically insignificant.

Key words: critical limb ischemia, angiosome, near-infrared spectroscopy, endovascular revascularization.

Įvadas

Periferinė arterijų liga (PAL) – tai aterosklerozinė liga, sukelianti apatinių galūnių kraujagyslių okliuziją. Nepakankama kraujo tėkmė ir audinių perfuzija kojose sukelia skausmą ir funkcijos sutrikimų. Negydoma liga gali progresuoti į kritinę galūnių išemiją [1]. Audinių išemijai vertinti taikomi metodai remiasi kraujo tėkmės, o ne audinių perfuzijos matavimu [2, 3], tačiau, siekiant geresnių kritinės galūnių išemijos gydymo rezultatų, reikėtų matuoti abu parametrus (kraujo tėkmę ir audinių perfuziją) – net ir sėkmingai atkūrus kraujotaką magistralinėje kraujagyslėje audinių perfuzija pagerėja ne visada [3, 4]. Audinių perfuzijos vertinimas ypač svarbus tam tikroms pacientų grupėms, pavyzdžiui, sergantiesiems cukriniu diabetu ar inkstų funkcijos nepakankamumu. Neretai šių pacientų audinių perfuzija mažėja išliekant nepakitusiai kraujo tėkmei [5–7]. Kritinė galūnių išemija gali būti gydoma atvirosios operacijos metu arba taikant endovaskulinį gydymą, atsižvelgiant į bendrąją paciento riziką, išemijos stadiją ir pažeistų kraujagyslių anatomiją [2]. Atvirosios operacijos metu distalinis šunto galas siuvamas į anatomiškai geriausiai tam tinkamą arteriją. Kartais po rekonstrukcinės operacijos, esant reikšmingų kolateralių trūkumų tarp revaskuliarizuotos arterijos ir lokalaus išemijos ploto, išlieka žaizdų progresavimo ir amputacijos rizika [8]. Išpopuliarėjus endovaskulinėms inter-

vencijoms, angiosomų principas įgavo klinikinę prasmę, nes endovaskulinė technika leidžia tiksliai atkurti kraujotaką į išemijos pažeistus audinius, remiantis angiosomų koncepcija, t. y. revaskuliarizuoti būtent tą kraujagyslę, kuri maitina pažeistą plotą [9]. Pagrindinis endovaskulinių procedūrų trūkumas – didelis restenozių ir reokliuzijų dažnis, siekiantis daugiau negu 41–64 proc. per metus [10, 11]. Šiandien nėra aišku, ar kraujotakos atkūrimas pagal angiosomas lemia geresnius ilgalaikius rezultatus [12, 13]. Pristatomo tyrimo tikslas – palyginti audinių oksigenacijos pokyčius išeminėje zonoje, endovaskuliniu būdu atkūrus kraujotaką tiesiogiai pagal angiosomą ir netiesiogiai.

Metodai

Leidimą atlikti šį mokslinį tyrimą suteikė Vilniaus regioninis biomedicininių tyrimų etikos komitetas 2017 m. gruodžio 5 d. (leidimo numeris 158200-17-981-482). 2019 m. balandžio 2 d. klinikinis tyrimas užregistruotas adresu *clinicaltrials.gov*, jam suteiktas registracijos numeris NCT03898869. Visi pacientai pasirašė informuoto asmens sutikimo formą.

Klinikinis tyrimas buvo atliekamas neuniversitetinėje tretinio lygio paslaugas teikiančioje ligoninėje – Vilniaus miesto klinikinėje ligoninėje, Kraujagyslių chirurgijos skyriuje. Tyrimas pradėtas 2019 m. balandžio 3 d., baigtas 2020 m. rugsėjo 7 d. Tyrimo tipas – perspektyvusis stebimasis tyrimas.

Pacientai buvo atrinkti pagal griežtus įtraukimo į tyrimą ir atmetimo kriterijus.

Įtraukimo kriterijai:

- Amžius – 55–95 m.
- Kritinės galūnių išemijos stadija – 4–5 Rutherfordo kategorija.
- Lėtinė visiška okliuzija arterijose žemiau kelių.
- Suplanuota revaskuliarizacija bent vienoje arterijoje žemiau kelio.
- Nereikalinga intervencija arterijose virš kelių.

Atmetimo kriterijai:

- Odos ligos, dėl kurių negalima tiksliai išmatuoti deguonies saturacijos sensoriais.
- Numatoma gyvenimo trukmė mažesnė negu 12 mėn.Neišvengiama amputacija virš kulkšnies.
- Kraujo deguonies saturacija – mažiau negu 85 proc.Endovaskulinę rekanalizaciją atliko vienas kraujagyslių chirurgas, naudodamas antegradinį, ipsilateralinį priėjimą ir, esant būtinybei, retrogradinę pėdos punkciją.

Visiems pacientams atliktas standartinis klinikinis ir laboratorinis tyrimas. Pacientų išeminės žaizdos vertintos naudojant WIfI (angl. *wound*, *ischemia*, *foot infection*) klasifikaciją [14]. Ši klasifikacija paremta žaizdos išplitimo įvertinimu, išemijos lygio nustatymu matuojant kulkšnies ir žasto indeksą bei infekcijos identifikavimu. Endovaskulinės intervencijos atliktos operacinėje, turinčioje *Innova 4100*, *GE* įrangą. Kulkšnies ir žasto indeksas matuotas *Dopplex® Ankle Brachial Pressure Index Kit* su EZ8 8MHz davikliu, *Huntleigh*. Deguonies saturacija ir gyvybiniai parametrai registruoti B40 *Patient Monitor*, *GE*. Visos procedūros atliktos pagal ligoninėje galiojančius protokolus (heparinizacija operacijos metu, dviguba antiagregacinė terapija 3 mėn. po procedūros). Trumpai veikiantys vazodilatatoriai naudoti tik atliekant distalinę punkciją. Šie medikamentai neturėjo įtakos nei pradiniams, nei galutiniams matavimams.

Oksigenacijos pokyčiai išemijos zonoje buvo matuojami naudojant Invos oksimetrą (*Somanetics* / *Medtronic*). Kiekvienam pacientui naudoti trys sensoriai. Du sensoriai buvo klijuojami ant sveikos odos, 2–3 cm nuo išeminės žaizdos krašto, o referencinis sensorius klijuotas šalia dešiniojo raktikaulio. Regioninė deguonies saturacija (rSO_2) buvo fiksuojama kas 6 sekundes. Po kiekvienos procedūros oksimetro duomenys buvo išsaugomi ir apdorojami naudojant *Excel v16.42*, *Microsoft*. Apskaičiuotas kiekvieno sensoriaus pirmų ir paskutinių 50 matavimų vidurkis. Revaskuliarizacijai įvertinti naudota formulė:

$$\text{Effect} = \left(\frac{\frac{(M1\alpha + M2\alpha) - (M1\omega + M2\omega)}{2} - (MR\alpha - MR\omega)}{\frac{M1\alpha + M2\alpha}{2}} - 1 \right) * 100$$

$M_{1\alpha}$ – pirmo sensoriaus pirmų 50 matavimų vidurkis (prieš revaskuliarizaciją);
$M_{2\alpha}$ – antro sensoriaus pirmų 50 matavimų vidurkis (prieš revaskuliarizaciją);
$M_{1\omega}$ – pirmo sensoriaus paskutinių 50 matavimų vidurkis (po revaskuliarizacijos);
$M_{2\omega}$ – antro sensoriaus paskutinių 50 matavimų vidurkis (po revaskuliarizacijos);
$M_{R\alpha}$ – referencinio sensoriaus pirmų 50 matavimų vidurkis (prieš revaskuliarizaciją);
$M_{R\omega}$ – referencinio sensoriaus paskutinių 50 matavimų vidurkis (po revaskuliarizacijos).

Statistiniai skaičiavimai atlikti naudojant SPSS 26.0 (IBM, Armonk, NY) programą ir *GPower* programos 3.1 versiją. Gauso pasiskirstymas ir duomenų homogeniškumas patvirtinti naudojant Shapiro ir Wilko bei Levene testus. Duomenys pateikiami naudojant standartinį nuokrypį (angl. *standard deviation*, ±SD) arba interkvartilinį intervalą (25–75 %) (angl. *interquartile range*, IQR). Statistinis reikšmingumas vertintas Stjudento t testu, kai duomenys pasiskirstė normaliai, ir Vilkoksono kriterijumi, kai duomenys pasiskirstė nenormaliai. Atskirų kategorijų kintamieji taip pat vertinti Fišerio testu. Skirtumas laikytas statistiškai reikšmingu, kai p vertė buvo <0,05.

Rezultatai

Klinikiniame tyrime dalyvavo 30 pacientų. 17 (57 %) pacientų buvo vyrai, vidutinis tyrime dalyvavusių pacientų amžius – 75 metai. 17 (53 %) pacientų sirgo cukriniu diabetu, 10 (33 %) pacientų buvo taikoma pakaitinė inkstų terapija (1 lentelė). Pirminiai klinikiniai duomenys, fiksuoti procedūros pradžioje, pateikiami 2 lentelėje. Vartojami vaistai nurodyti 3 lentelėje.

1 lentelė. Demografiniai duomenys

Kintamieji	Kiekis (%) arba mediana, ±SD
Pacientai	30
Amžius, metai	74,7±11,2
Vyrai	17 (57 %)
Europidai	30 (100 %)
Cukrinis diabetas	16 (53 %)
Paskutinės stadijos lėtinė inkstų liga	10 (33 %)
Hipertenzija	24 (80 %)
Koronarinė širdies liga	21 (70 %)
Buvęs miokardo infarktas	11 (36,7 %)

2 lentelė. Pirminiai klinikiniai duomenys

Kintamieji	Kiekis (%) arba mediana, ±SD
Kritinė galūnių išemija, 5 Rutherfordo kategorija	30 (100 %)
Lėtinė visiška okliuzija žemiau kelio	30 (100 %)
Buvusi atviroji operacija toje pačioje kojoje	3 (10 %)
Buvusi endovaskulinė procedūra toje pačioje kojoje	13 (43 %)

Kintamieji	Kiekis (%) arba mediana, ±SD
Buvusios mažosios amputacijos toje pačioje kojoje	6 (20 %)
Padidėjęs CRB hospitalizavimo metu	12 (40 %)
Leukocitozė hospitalizavimo metu	10 (33 %)
WIfI, W2	14 (46 %)
WIfI, I2	15 (50 %)
WIfI, fI1	12 (40 %)
KŽI (20 pacientų)	0,6 [0,21]
Lėtinė visiška okliuzija, planuojamas blauzdos arterijų gydymas	30 (100 %)
Kraujospūdis (sistolinis) procedūros pradžioje	154±19,4
Deguonies saturacija kraujyje, %	94±2,5

CRB – C reaktyvusis baltymas; WIfI – žaizdų klasifikacija, kurioje W2 yra gili gangrena, apimanti pirštus; I2 – kojos išemija, kai KŽI 0,4–0,59; fI1 – nedidelis aplinkinis uždegimas iki 2 cm; KŽI – kulkšnies ir žasto indeksas.

3 lentelė. Vartojami vaistai

Statinai	11 (36,7 %)
Antikoaguliantai	11 (36,7 %)
Antihipertenziniai vaistai	24 (80 %)
Antiagregantai	21 (70 %)

Pacientų išeminės žaizdos priklausymas vyraujančiai angiosomai pateiktas 4 lentelėje.

4 lentelė. Pažeidimai pagal angiosomas

Angiosomą maitinanti kraujagyslė	Dažnis	Procentai
Priekinė blauzdos arterija	16	53,3 %
Užpakalinė blauzdos arterija	8	26,7 %
Šeivinė arterija	6	20,0 %
Iš viso	30	100 %

Tyrimo metu 30 pacientų atlikta 30 endovaskulinių intervencijų, revaskuliarizuotos 44 kraujagyslės (5 lentelė).

5 lentelė. Revaskuliarizacijų pasiskirstymas

Revaskuliarizuotos kraujagyslės	Dažnis	Procentai
Priekinė blauzdos arterija	21	47,7 %
Užpakalinė blauzdos arterija	10	22,7 %
Šeivinė arterija	8	18,2 %
Blauzdos šeivinis kamienas	2	4,5 %
Pakinklio arterija	3	6,8 %
Iš viso	44	100 %

Tyrimo metu 15 pacientų (50 %) kraujotaka buvo atkurta pagal angiosomą, tokiai pat daliai pacientų (50 %) – ne pagal angiosomą. Lyginti šių dviejų grupių audinių oksigenacijos pokyčiai operacijos metu. Didesnis oksigenacijos pokytis pastebėtas pacientų, kuriems atlikta revaskuliarizacija pagal angiosomą, grupėje (6 lentelė), bet statistiškai reikšmingo oksigenacijos skirtumo tarp grupių nenustatyta (nepriklausomos grupės t testas, p = 0,544).

6 lentelė. NIRS pokytis tarp grupių

Revaskuliarizacijos grupės	**Dažnis**	**NIRS padidėjimo vidurkis, %**	**Standartinė derivacija,** ±SD
Revaskuliarizacija pagal angiosomą	15	23,160	22,5719
Revaskuliarizacija ne pagal angiosomą	15	29,020	29,2977

NIRS (angl. *near-infrared spectroscopy*) – artimųjų infraraudonųjų spindulių spektroskopija.

Atlikta galios analizė įvertinti, kiek pacientų turėtų dalyvauti tyrime, kad jo rezultatai būtų statistiškai patikimi. Jei α klaidos tikimybė būtų 0,05, o 1-β klaidos tikimybė būtų 0,8, tyrime turėtų dalyvauti 504 tiriamieji.

Diskusija

Klinikiniame tyrime audinių oksigenacijos pokyčiui išeminėse zonose skirtingose grupėse vertinti pasirinkta artimųjų infraraudonųjų spindulių spektroskopija. Kiek žinoma, tai pirmas kartas, kai NIRS metodas taikomas tokiomis aplinkybėmis.

Neinvazinė NIRS sistema susideda iš monitoriaus ir lanksčių sensorių, kurie turi šviesos šaltinį ir du šviesą priimančius fotodetektorius. Šviesos šaltiniai generuoja skirtingų ilgių artimųjų infraraudonųjų spindulių bangas, kurios turi skirtingą penetracijos gylį bei skirtingai sugeriamos oksi- ir deoksihemoglobino. Pagal tai skaičiuojama audinių oksigenacija maždaug 2 cm gylyje. NIRS sistemos skleidžiami spinduliai nėra pavojingi audiniams ir nesukelia terminio efekto, todėl gali būti naudojami ilgą laiką, pavyzdžiui, visos operacijos metu.

NIRS sensorių absoliučiosioms vertėms turi įtakos mioglobinas, lipidai, vandens kiekis, todėl audinių oksigenacijos reikšmės yra individualios kiekvienam pacientui, jas sunku lyginti tarpusavyje [15, 16]. Audinių perfuziją galima išmatuoti ir kitais būdais, pavyzdžiui, matuojant transkutaninį deguonies slėgį (TcPO2), naudojant 2D perfuzijos angiografiją, mikrodeguonies sensorius (MOXYs), hiperspektrinį vaizdavimą. Audinių perfuzijos matavimo poreikis didelis, kasmet atsiranda naujų perfuzijos matavimo būdų, tačiau vadinamojo auksinio standarto kol kas nėra [2].

1987 m. Ianas Tayloras ir bendraautoriai pradėjo vartoti *angiosomos* sąvoką. Angiosoma apibrėžiama kaip audinių, apimančių odą, poodį, fasciją, raumenis ir kaulus, visuma, maitinama vienos arterijos ir turinti tam tikrą drenuojančią veną. Žinoma, kad kulkšnį ir pėdą sudaro šešios skirtingos angiosomos, maitinamos trijų žemiau kelio esančių pagrindinių kraujagyslių: priekinės ir užpakalinės blauzdos arterijų bei šeivinės arterijos [17, 9].

Revaskuliarizacija, atsižvelgiant į angiosomas, nėra laikoma kritinės galūnių išemijos gydymo standartu, tačiau mokslinėje literatūroje yra straipsnių, kuriuose pateikiami šio gydymo metodo privalumai. Autoriai nurodo, kad revaskuliarizacija pagal angiosomas siejama su geresniu žaizdų gijimu ir didesne galūnės išsaugojimo tikimybe [18, 19]. Atviųjų operacijų metu siekiant atkurti kraujotaką dažniausiai nėra laikomasi angiosomų sampratos, nes distalinei šunto įsiuvimo vietai pasirenkama anatomiškai tinkamiausia kraujagyslė, kuri nebūtinai tiekia kraują į išemijos paveiktą angiosomą. Vis dėlto netiesioginė revaskuliarizacija gali būti tinkama, jei yra susiformavęs pakankamas kolateralių tinklas. Priešingai negu operuojant atvirai, taikant endovaskulinį

gydymą galima tiesiogiai atkurti kraujotaką į išemišką zoną ir revaskuliarizuoti daugiau negu vieną arteriją tos pačios intervencijos metu [3]. Svarbu tai, kad, sergant cukriniu diabetu ar inkstų funkcijos nepakankamumu, kolateralinių kraujagyslių formavimasis būna nepakankamas. Kai kurių autorių manymu, tinkamiausias būdas pasiekti geriausio pooperacinio rezultato yra tiesioginė revaskuliarizacija, remiantis angiosomų samprata [20].

Straipsnyje pristatomu tyrimu pirmą kartą lygintas tiesioginio ir netiesioginio kraujotakos atkūrimo efektas išeminiams audiniams, matuojant juose deguonies kiekį. Gautas mažas oksigenacijos pokyčio tiriamųjų grupėse skirtumas galimai paaiškina, kodėl revaskuliarizacija pagal angiosomas nėra prigijusi kaip standartinė praktika daugelyje pasaulio klinikų.

Išvados

Klinikinio tyrimo metu audinių oksigenacijos pokytis atkuriant kraujotaką pagal angiosomą mažai skyrėsi nuo audinių oksigenacijos pokyčio atkuriant kraujotaką ne pagal angiosomą. Skirtumas nebuvo statistiškai reikšmingas. Audinių perfuzijai matuoti nėra vadinamojo auksinio standarto, todėl šio tyrimo rezultatus tikslinga patikrinti kitais audinių perfuzijos matavimo būdais, pavyzdžiui, matuojant transkutaninį deguonies slėgį pooperaciniu laikotarpiu.

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Original Research

Measurement of Revascularization Effect Using Near Infrared Spectroscopy in Below the Knee Arteries

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Abstract

Objectives: Current methods evaluating tissue ischemia are based mainly on evaluating blood flow and not tissue perfusion. However, diabetes mainly affects small vessels and blood flow evaluation is insufficient. The aim of the trial was to evaluate the feasibility of NIRS in measuring perfusion changes during chronic total occlusion (CTO) revascularization in below the knee (BTK) arteries. **Methods and Material**: A prospective observational study was performed. During the endovascular revascularization procedure, tissue oxygenation changes were measured using three NIRS sensors. Postoperative angiographies and 30 days wound healing was evaluated. **Results**: The study enrolled 30 patients with chronic limb threatening ischemia, occluded below the knee arteries, Rutherford 5. Mean age 74.7 $\pm$ 11.2 years, 16 (53%) of the patients had diabetes mellitus, 10 (33%) had end-stage renal disease. A statistically significant NIRS rSO_2 increase was observed on sensors near the wound after the revascularization, $p = 0.001$. Thirty days follow-up visits included 27 patients, because 3 patients had died. Comparing good wound healing group with poor wound healing group intraoperative NIRS rSO_2 increase difference was statistically significant, $p = 0.017$. **Conclusions**: The study confirmed tissue perfusion increase could be detected using NIRS during revascularization of below the knee arteries. An intraoperative increase of NIRS rSO_2 proved to predict wound healing results.

Keywords: near-infrared spectroscopy; blood perfusion; wound healing; chronic limb-threatening ischemia; below the knee; chronic total occlusion

Type of Research: Single center prospective observational study.

Key Findings: Tissue perfusion increase was detected using NIRS during revascularization of below the knee arteries in 30 patients. NIRS was superior in predicting wound healing compared to a blinded angiography evaluation.

Take home Message: Tissue perfusion measurement is of increasing importance due to growing incidence of small vessel disease, which are resulted by diabetes and end stage renal disease. However, there is no validated method to evaluate it. NIRS showed promising intraoperative monitoring results in a very restricted cohort.

Summary: NIRS is feasible method for detecting tissue perfusion changes during endovascular revascularization of BTK and BTA arteries. This proof of concept does not translate into clinical practice with existing devices in the market.

1. Introduction

Chronic limb-threatening ischemia (CLTI) is an end-stage of peripheral artery disease (PAD), which includes a broad and heterogeneous group of patients [1]. Because of the aging society and the increasing prevalence of diabetes mellitus, the altered vascular bed shifts from aortoiliac to below the knee (BTK) and below the ankle (BTA) [2]. The new term "small artery disease" (SAD) is coming to stage not as a subgroup of PAD but more as an independent disease caused by medial arterial calcification [3,4]. This increases the importance of blood perfusion measurement.

Current methods evaluating tissue ischemia are based mainly on assessing blood flow and not blood perfusion [1, 5]. Palpation of pulses, ankle brachial index (ABI), duplex ultrasound, computed tomography angiography (CTA), magnetic resonance angiography (MRA), and some other methods evaluate blood flow exclusively. This is suitable for diagnosis and prognosis of a big artery disease (aortoiliac, above the knee). However, blood flow evaluation is less valuable in BTK or below the ankle (BTA) disease, especially when the toe pressure cannot be assessed [1]. Furthermore, even in cases with unaltered blood flow, patients could have ischemic wounds due to poor tissue perfusion. Several pathophysiological mechanisms come into play in diabetic patients. Diabetic polyneuropathy leads to sympa-

thetic denervation, causing increased capillary permeability and opening of arterio-venous shunts [6,7]. Thickening of the basal membrane causes arteriolar hyalinosis and impairs vasodilation [8].

Blood flow and tissue perfusion mismatch were discussed in the literature extensively [9,10], however, there is still no valid method to evaluate perfusion. The main issue with blood perfusion measurement is a high variability among patients because of many confounding factors [1]: blood pressure, oxygen saturation, heart ejection fraction, peripheral spasm, environmental temperature, etc. It causes high variability in measurements even among the patients without PAD/SAD. The only partial exception is a $TcPO_2$ measurement, with a negotiable 40 mmHg cut-off value [11–13], but it is inconvenient and time consuming.

Another issue regarding the evaluation of tissue perfusion is the lack of the reference standard. This turns into a validation problem of new techniques as tissue perfusion results should not be validated according to blood flow measurement. However, tissue perfusion results could be compared to the clinical outcome. Wound healing is a slow process, and that particular cohort of patients is very fragile. One-year cumulative amputation risk for amputation and death in a COMPASS trial was 23% and 9%, respectively [14]; yearly reintervention rate could be up to 30% [15]. That is why blood perfusion comparison to a long-lasting follow-up is questionable in this rapidly changing population.

A lot of new blood perfusion in tissues evaluating techniques have emerged recently, trying to prove their value: contrast-enhanced ultrasound [16–18]; MRI perfusion imaging [19–21]; hyperspectral imaging [22,23]; laser doppler perfusion monitoring [12]; laser speckle contrast imaging [24,25]; near-infrared spectroscopy [26–29]; near-infrared fluorescence imaging with indocyanine green [30,31]; spectrophotometry [32]; vascular optical tomography imaging [33]; photoacoustic imaging; micro-oxygen sensors [34] and some other emerging techniques. However scientific data is scarce and only two of the studies mentioned above have included more than 100 patients.

NIRS devices use several diodes of different wavelength, which has different penetration and absorption patterns by oxygenated and deoxygenated hemoglobin. Invos Oximeter (Somanetics/Medtronic) uses two diodes: 800 nm for oxygenated and deoxygenated hemoglobin and 760 nm for deoxygenated hemoglobin. The calculated measurement reflects tissue oxygenation. While tissue perfusion is not the same as tissue oxygenation, in this setting, where ischemic wound is associated with occluded BTK/BTA arteries, intraoperative changes of tissue oxygenation after revascularization reflect changes in tissue perfusion.

In our vascular center more than 800 lower limb endovascular interventions a year are performed. Having some prior not published expertise, which is entirely in line with the only published NIRS PAD clinical study by de Boezeman *et al*. [35], it was decided to investigate NIRS in a well-controlled clinical environment, as any variability in clinical cases (claudication vs. CLTI), intervention mode (open surgical vs. endovascular vs. BMT), anatomical site of lesion (aortoiliac vs. ATK vs. BTK), severe comorbidities, significantly affecting oxygen saturation, lead to very scattered results which are impossible to conclude in trials with a volume below ~1000 cases. An intraoperative measurement with a controlled environment as well as diminished interpatient variability in a small trial group could be a valuable proof of concept. If it fails, the possible benefit of NIRS measurement in a real-life scenario could be close to zero.

NIRS was evaluated in some wound healing clinical trials [36–38]. These trials showed oxygenated hemoglobin concentration differences in good versus poor healing wounds, however the wounds were not ischemic [37,38], or only several of them ischemic [36]. This proves the ability to detect tissue oxygen changes using NIRS, however the results are scattered due to different ethiology of wounds and can hardly be translated to clinical practice.

Several systematic reviews were published summarizing possible benefits and shortcomings of NIRS in PAD evaluation [39,40]. Despite the ability to detect PAD more precisely in some clinical scenarios, the main shortcoming was variability of the results which limited the clinical usage.

The aim of the study was to test if NIRS can detect the intraoperative increase of tissue oxygenation and if the elevation of NIRS rSO_2 predicts wound healing in patients with CLTI and occlusion of below the knee arteries.

2. Materials and Methods

Vilnius Regional Biomedical Research Ethics Committee approved this study on Dec. 5, 2017, registration number 158200-17-981-482. The study was registered in clinicaltrials.gov on Apr. 2, 2019, registration number NCT03898869. Patients were included after obtaining informed consent.

The study was conducted in a tertiary non-university Vilniaus Miesto Klinikine Hospital, department of Vascular Surgery. The study was started Apr. 3, 2019, finished Sep. 7, 2020.

2.1 Patients

To avoid variability in measurements, strict inclusion and exclusion criteria were defined:

Inclusions criteria

- All comers PAD patients 55–95 years old;
- CLTI Rutherford V–VI;
- CTO below the knee;
- At least one artery below the knee was planned to be revascularized;
- No need for intervention in above the knee arteries.

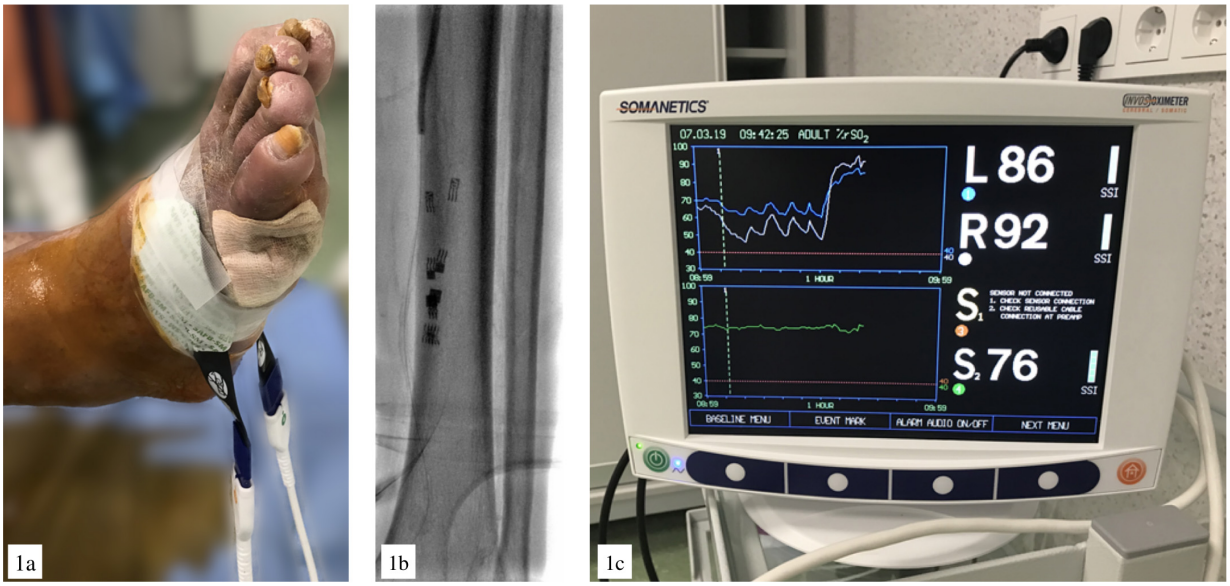

Fig. 1. NIRS application during revascularization procedure. (a) Sensor placement near the wound. (b) X-ray view. (c) NIRS screen.

Exclusion criteria

- Skin diseases preventing the use of NIRS;
- Life expectancy less than 12 months;
- Unavoidable amputation above the ankle;
- Systemic blood oxygen saturation below 85%.

All patients underwent standard clinical and laboratory investigation. The wounds were assessed according to WIfI classification [41]. The diagnosis of chronic total occlusion (CTO) was based on the results of angiography performed either at referring hospital or at the time of admission in our center.

2.2 Procedure and Measurements

Endovascular BTK/BTA revascularization procedure was performed by a single vascular surgeon using antegrade ipsilateral groin approach and retrograde pedal puncture when needed. All procedures were performed according to standard of practice (heparinization during the procedure, dual antiplatelet therapy for 3 months after the procedure). Short acting vasodilators were used only in the cases where distal puncture was needed. These medicines had no impact neither for initial measurements nor for final measurements.

All procedures were performed in an operating room equipped with Innova 4100, GE (Boston, Massachusetts, US). Postoperative images were anonymized and blindly evaluated by an independent interventional radiologist using Horos v3.3.6 (Annapolis, MD, USA). Technical angiographic success was scored 1 or 2, where 1—ranged from not successful recanalization to partialy successful recanalization, but without preservation of direct flow to pedal arch; 2—successful recanalization with full blood flow restoration through the pedal arch.

NIRS was measured using Invos Oximeter, Somanetics/Medtronic (Dublin, Ireland). Two probes were placed near the ischemic wound on muscular beds, and one reference probe was set on the pectoral muscle (Fig. 1a). Two sensors near the wound were placed on healthy skin, approximately 2–3 cm from ulcer margin. Because of sensors detecting oxygenation changes in ~2 cm depth, they were not placed over the tibial bone and over the bony prominences.

Despite the sensors were placed in the same region where revascularization was performed, they did not interfere with the X-ray view (Fig. 1b). The balloon inflation effect could be visualized on the NIRS screen (Fig. 1c).

After the procedure, NIRS data was downloaded and post processed using Excel v16.42, Microsoft (Redmond, WA, USA). rSO_2 was recorded every 6 seconds. The mean of the first and the last 50 measurements of each sensor was calculated. The effect of revascularization was calculated using the formula below. The main goal was to zero the impact of fluctuations in systemic circulation using the reference sensor on the shoulder.

$$\text{Effect} = \left(\frac{\frac{(M1\alpha + M2\alpha) - (M1\omega + M2\omega)}{2} - (MR\alpha - MR\omega)}{\frac{M1\alpha + M2\alpha}{2}} - 1 \right) * 100$$

$M_{1\alpha}$ — mean of the first 50 measurements on sensor 1 (before revascularization); $M_{2\alpha}$ — mean of the first 50 measurements on sensor 2 (before revascularization); $M_{1\omega}$ — mean of the last 50 measurements on sensor 1 (after revascularization); $M_{2\omega}$ — mean of the last 50 measurements on sensor 2 (after revascularization); $M_{R\alpha}$ — mean of the first 50 measurements on reference sensor (before revascularization); $M_{R\omega}$ — mean of the last 50 measurements on reference sensor (after revascularization).

A right shoulder was used for baseline sensor. The other leg is usually altered by the same disease. The blood perfusion in arms might be altered by prior dialysis access surgery, as end stage renal disease is quite abundant in this patient cohort. That is why a shoulder was chosen as a baseline place.

Vital signs and oxygen saturation on the index finger were monitored using B40 Patient Monitor, GE (Boston, Massachusetts, USA).

The final anonymized angiographic results from all 30 subjects were evaluated by an independent radiologist and patients were assigned into two groups. The first group—suboptimal angiographic result, when the blood flow to the pedal arch was not restored. The second group — good angiographic result with blood flow restoration to the pedal arch.

ABI was measured using Dopplex® Ankle Brachial Pressure Index Kit with EZ8 8MHz Probe, Huntleigh (Cardiff, Wales, UK).

2.3 Follow-Up

A follow-up visit was set up 30 days after the discharge for each patient. Wounds were reassessed using WIfI classification by the same vascular surgeon. Wound healing after one month was evaluated using WIfI classification. Because of small number of patients, scattered initial wound characteristics and different healing patterns, the second type of grading was used, based on healing pattern as 1 or 2, where 1—no improvement or slight improvement; 2—wound is healed or is healing rapidly and there is tendency for complete heal in the near future.

2.4 Statistical Analysis

Statistics were performed using SPSS 26.0 (IBM, Armonk, NY, USA) and power calculations were performed using GPower version 3.1 (HHU, Dusseldorf, Germany). The Gaussian distribution and homogeneity of variance of the data were confirmed using Shapiro-Wilk and Levene tests. Data are presented as the mean ± SD for normal distributed values, otherwise median and interquartile range (25 and 75 percentile) (IQR). Outliers were defined as more than mean ± 3SD and excluded from further analysis. Statistical significance was assessed using Student's *t*-test for normal distributed data, the Wilcoxon signed rank test for continuous non normal distributed variables and Fisher's exact test for categorical variables. The difference between samples was considered statistically significant if the *p* value was less than 0.05.

2.5 Power Analysis

There was no preliminary data we could use to perform power analysis before the trial. The sample size was chosen to be twice as big as the cohort of the only previous clinical trial dealing with intraoperative endovascular NIRS measurement [35] and the only trial dealing with intraoperative open surgery NIRS measurement. The sample size was also based on other blood perfusion tests (hyperspectral imaging, laser doppler perfusion monitoring, near-infrared fluorescence imaging with indocyanine green, micro-oxygen sensors, etc.) listed previously.

The post-hoc Power analysis was performed after calculating the results. The sample size for matched pairs *T*-test with α error probability of 0.05 and Power (1 - β error probability) of 0.95 is 23 subjects to detect difference between preoperative and postoperative results. The sample size for independent groups *T*-test with α error probability of 0.05 and Power (1 - β error probability) of 0.8 is 38 subjects to detect difference between two patient groups based on postoperative results and different clinical outcomes.

3. Results

30 patients were enrolled into the study. There were 17 males (57%), the mean age of the patients was 74.7 ± 11.2 years. 16 patients (53%) had diabetes mellitus, 10 (33%) had end-stage renal disease (Table 1). All patients had chronic total occlusion below the knee and the ischemia was classified as Rutherford category V (Table 2). NIRS rSO_2 measurements and other intervention data that were collected during the procedure are depicted in Tables 2,3.

Table 1. Demographic data.

Variables	No. (%) or Mean ± SD
Study patients	30
Age, years	74.7 ± 11.2
Male	17 (57%)
Caucasian	30 (100%)
Diabetes mellitus	16 (53%)
End stage renal disease	10 (33%)
Hypertension	24 (80%)
Coronary artery disease	21 (70%)

Statistically significant NIRS rSO_2 increase (Table 3) was observed on sensors near the wound after the reperfusion (paired samples *T*-test, $p = 0.001$). Statistically significant NIRS rSO_2 decrease during the procedure on reference sensor during the procedure (paired samples *T*-test, $p = 0.001$).

Independent anonymous evaluation of revascularization success was performed. The success was rated as suboptimal in 12 (40%) cases (group 1) and optimal in 18 (60%) cases (group 2).

Follow-Up

3 patients (10%) died during the first 30 days, therefore the follow up included 27 patients. Wound healing after 30 days was evaluated as poor in 9 patients (30%) and good in 18 patients (70%). Follow-up ABI median was 0.7 [0.2].

Patients with different angiographic revascularization

Table 2. Initial clinical data.

Variables	No. (%) or Mean ± SD
CLTI, Rutherford V	30 (100%)
CTO below the knee	30 (100%)
Concomitant SFA disease, requiring treatment	1 (3%)
Previous open surgery on index leg	3 (10%)
Previous endovascular intervention on index leg	13 (43%)
Previous minor amputations on index leg	6 (20%)
Elevated CRP on admission	12 (40%)
Increased WBC on admission	10 (33%)
WIfI, W2	14 (46%)
WifI, I2	15 (50%)
WifI, fI1	12 (40%)
ABI (20 patients)	0.6 [0.21]
CTO, intended to treat P3	1 (3%)
CTO, intended to treat distal to popliteal artery	30 (100%)
BP, systolic at the beginning of procedure	154 ± 19.4
Oxygen saturation, %	94 ± 2.5

CLTI, chronic limb threatening ischemia; CTO, chronic total occlusion; SFA, superficial femoral artery; CRP, C reactive protein; WBC, white blood cells; WIfI, the classification system proposed by the Society for Vascular Surgery (W, Wound; I, Ischaemia; fI, foot Infection); ABI, ankle brachial index; BP, blood pressure.

Table 3. Intervention data.

Sensor	NIRS rSO_2 before the reperfusion, Mean ± SD	NIRS rSO_2 after the reperfusion, Mean ± SD	*p* value
Sensor 1	58.0 ± 12.7	66.7 ± 11.6	0.001
Sensor 2	57.6 ± 12.7	67.1 ± 14.0	<0.001
Reference sensor	67.7 ± 11.3	63.1 ± 12.0	0.001

CTO, chronic total occlusion; NIRS, near infrared spectroscopy.

Table 4. Comparison of angiographic results and wound healing.

	Suboptimal angiographic result	Optimal angiographic result
Poor wound healing	4	5
Good wound healing	6	12

Fisher exact test used, $p = 0.683$.

Table 5. Comparison of NIRS rSO_2 change in different wound healing groups.

Poor wound healing		Good wound healing		
NIRS rSO_2 change after the revascularization, Mean ± SD	No. of patients	NIRS rSO_2 change after the revascularization, Mean ± SD	No. of patients	*p* value
13.6 ± 3.3	6	27.2 ± 25.2	18	0.017

Student's *t*-test used for comparison.

NIRS, near infrared spectroscopy.

success were stratified by their clinical outcome (the course of wound healing) (Table 4). There was no relationship between the angiographic success and wound healing categories (Fisher exact test, $p = 0.683$). Initial and final ABI, initial and final NIRS rSO_2 values, current comorbidities did not correlate with wound healing also.

Comparing good wound healing group vs. poor wound healing group intraoperative NIRS rSO_2 increase difference was statistically significant, $p = 0.017$ (Table 5). Three statistical outliners were excluded from calculations.

4. Discussion

NIRS is a non-invasive method which is not harmful to tissue even if applied for a longer period of time [42]. In contrast to other methods measuring tissue perfusion such as $TcPO_2$, NIRS does not require skin to be heated prior to measuring tissue perfusion and it is not so operator depen-

dant as hyperspectral imaging [1,22]. Compared to microoxygen sensors (MOXY), NIRS appears to be a less expensive, non invasive and easier to perform technique [34]. Also, application of NIRS does not require additional contrast media and standartized protocol as it must be done while using 2D perfusion angiography [43].

INVOS™ Cerebral/Somatic Oximetry device, which was used in this study, is not the most optimal NIRS device for detecting peripheral tissue perfusion. It was chosen because it has a CE Mark and is broadly available in clinical practice.

To the best of our knowledge this is the second study in the world evaluating intraoperative NIRS results. The first study, conducted by Boezeman *et al*. [35], showed no NIRS rSO_2 increase after the revascularization. However, that study included only 14 patients, 43% of them were without gangrene, 79% of the lesions were above the knee, no data was obtained comparing stenosis versus CTO.

Our experience evaluating blood perfusion using NIRS outside this study patients replicated the findings published by Boezeman *et al*. [35]. Small intraprocedural NIRS rSO_2 increase is influenced by numerous factors, such as spasm following introducer sheath insertion, blood pressure fluctuations, patient hyperventilation, etc. The most significant NIRS rSO_2 increase was observed after the direct blood flow restoration to the target area. Therefore, an assumption was made that if NIRS measurement could prove its value, it would do it in specifically controlled environment.

A significant increase in NIRS rSO_2 was demonstrated after restoration of blood perfusion in the current study. This lets us think that NIRS can be used for intraoperative blood perfusion measuring in patients with CTO and below the knee occlusion. Moreover, a higher increase in NIRS rSO_2 after revascularization was associated with better wound healing. In this setting, the increase in NIRS rSO_2 served as prognostic marker of wound healing and even outperformed the predictive potential of independent angiographic evaluation of revascularization.

The first approach to test tissue perfusion during described revascularization procedure proved to be successful. However, it is a far cry from everyday day use in clinical practice. The next step could be validating this technology comparing with $TcPO_2$ measurements before and after the procedure, repeating NIRS and $TcPO_2$ on 30-day follow-up visit.

5. Limitations of Technology

All calculations were made after postprocessing of the data, where the baseline was connected to a reference sensor value. As baseline data is changing during the procedure, it is important to note that the current Invos Somanetics device uses a different formula and the results shown on screen are not straightforward.

The price of each single-use sensor is equal to the price of a PTA balloon. Using three sensors per procedure on a routine basis could increase the average procedure cost. On the other hand, even the small improvement in treatment strategy may contribute to huge savings in ulcer treatment. This was demonstrated by Weingarten *et al*. [44] with an earlier detection of wound healing failure using NIRS allowing to save more than 12,000 USD per patient.

The impact of severe local inflammation, lung and heart diseases affecting oxygen saturation, alter the measurements and might limit the usage of this technology.

6. Limitations of the Study

Despite rigorous inclusion criteria, an additional one could have been included. Severe local inflammation impacts the measurement, so fI 2 and 3, according to WIfI classification, could have been excluded.

The only validated tissue perfusion measurement $TcPO_2$ before and after the procedure could have been included in the comparison. We have not included it, as the primary idea was to put NIRS sensors as close to the wound as possible and $TcPO_2$ measurement has more defined areas. However, a future study comparing $TcPO_2$ and NIRS rSO_2 with a different patient group, giving more attention to the wound characteristics and location, could be planned. Some studies have compared NIRS and $TcPO_2$ [45] with promising results.

7. Future Perspectives

We see a potential of NIRS measurements in evaluating ischemic tissue perfusion. Possibility to revascularize one, two, or three BTK arteries is a nice option enabled by endovascular technique. However, a patient with CLTI is usually very fragile and the need to shorten the intervention is widely expressed. The ability to monitor tissue perfusion near the wound during the procedure and stop the procedure once required increase is achieved would be extremely valuable. Currently there are no devices certified for detection of tissue perfusion changes during revascularization. The need to postprocess data is a clear barrier for every day clinical use of existing devices. That is why, further adoption of this technology is limited to manufacturers of existing devices.

Positive results of this study set background for further investigation. Future studies are needed to assess the ability of NIRS to predict wound healing, minor and major amputation in larger patient cohorts.

8. Conclusions

NIRS is feasible method for detecting tissue perfusion changes during endovascular revascularization of BTK and BTA arteries. However, a dedicated device with a modified measurement technique is needed.

Author Contributions

Conception and study design—TB, KR. Data collection—GP, AR, VM, AS, GV. Data analysis and interpretation SŠ, VB, SU. Writing of the manuscript—TB, GP, AR, VM, VB, AS, GV, SŠ, SU, KR.

Ethics Approval and Consent to Participate

All subjects gave their informed consent for inclusion before they participated in the study. The study was conducted in accordance with the Declaration of Helsinki, and the protocol was approved by Vilnius Regional Biomedical Research Ethics Committee (approval number: 158200-17-981-482).

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Conflict of Interest

The authors declare no conflict of interest.

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Article

Oxygen Saturation Increase in Ischemic Wound Tissues after Direct and Indirect Revascularization

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Abstract: Background: The primary approach for treating ischemic wounds is restoring oxygen supply to the ischemic region. While direct angiosomal revascularization is often associated with better post-operative wound healing and limb salvage, its superiority over non-angiosomal revascularization remains controversial. This study aimed to compare intraoperative tissue oxygen saturation changes in ischemic zones following either direct or indirect revascularization in below-the-knee arteries. Methods: This prospective observational study included patients undergoing direct and indirect below-the-knee endovascular revascularizations. Assignment to the groups was not randomized. Near-infrared spectroscopy was used to monitor rSO2 changes near the ischemic wounds intraoperatively. The changes were compared between the groups. Results: 15 patients (50%) underwent direct angiosomal revascularization, while an equal number of patients underwent indirect revascularization. Overall, a statistically significant increase in regional oxygen saturation was observed after revascularization ($p = 0.001$). No statistically significant difference was found between the direct and indirect revascularization groups ($p = 0.619$). Conclusions: This study revealed a minor difference in the oxygen saturation increase between the angiosomal and non-angiosomal revascularization groups. Such a finding indicates that the clinical significance of angiosomal revascularization is negligible and might be concealed by confounding factors, such as the vessel diameter and outflow impact on the restenosis rate.

Keywords: ischemic wounds; chronic limb-threatening ischemia; chronic total occlusion; angiosome; near-infrared spectroscopy; direct revascularization; indirect revascularization

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1. Introduction

Despite many years of progress and scientific innovations in the field of wound healing, the burden of chronic wounds still has a relevant impact on healthcare costs and resource consumption [1,2]. It is reported that in the USA alone, chronic lower limb wounds affect up to 4.5 million people [3], while in developed countries, the financial commitment to care for such wounds makes up to 3% of the overall healthcare budget [4]. Notably, chronic wounds derive from various causative factors, with vascular pathologies, particularly arterial and venous leg ulcers, standing out as the most prevalent and economically impactful [5]. Chronic wounds significantly contribute to reduced life quality and cause impairment or loss of function and even death [3]. Among the spectrum of chronic wounds, ischemic wounds induced by peripheral arterial disease (PAD) are characterized by the highest reported mortality rate [6]. However, regardless of the specific etiology of the wound, one of the most crucial elements for wound healing is the state of the vasculature. Inadequate tissue perfusion disrupts the supply of nutrients and other factors that are critically important for wound healing, leading to reduced collagen deposition, impaired angiogenesis,

and poor epithelialization [7]. Under physiological conditions, relative hypoxia induces angiogenesis and activates several important factors, such as vascular endothelial growth factor (VEGF), transforming growth factor-beta (TGF-β), and platelet-derived growth factor (PDGF), which are vital elements for the wound-healing process [8]. However, in cases of severe ischemia, the response to hypoxia becomes aberrant, causing dysfunctions in protein induction pathways and ultimately resulting in the formation of non-healing wounds [5]. Therefore, the primary approach to healing arterial wounds is restoring the blood supply to the ischemic region, which can be achieved by performing open surgical repair and endovascular interventions [9]. The latter method gives an opportunity to revascularize not only one but several different arteries during the same intervention. Moreover, the endovascular technique allows for restoring the blood flow directly to the artery supplying the ischemic zone, based on the angiosome concept, even when the run-off vessel is very poor [10]. However, the clinical effect of revascularizing a vessel with a poor run-off still remains undetermined.

Direct angiosomal revascularization is reported to have better post-operative wound healing and limb salvage results [11,12]. Therefore, in clinical practice, it is recommended to consider performing direct revascularization first in patients with significant wounds [9]. It is also suggested that direct revascularization is especially valuable for patients with diabetic foot ulcers since they are known to have poorly developed infrapopliteal arterial collaterals [13], while in the presence of good collateral vessels, direct revascularization loses its primary value [14]. Moreover, performing direct revascularization is not always achievable, due to incompatible anatomy or technical reasons. When angiosomal revascularization is not possible, the only option to improve blood perfusion in ischemic tissues is to revascularize the most technically approachable artery with the best run-off. The decision to perform indirect revascularization as well as choosing the most suitable artery for revascularization in different clinical scenarios fully depend on the doctor's opinion. Despite endovascular below-the-knee revascularizations being widely performed in everyday clinical practice, there is still debate about whether direct angiosomal revascularization is superior to indirect [15].

While it has been established that revascularization is the most straightforward pathway for healing arterial chronic wounds, the lack of a suitable method to quantitatively assess the efficacy of revascularization, to this day, remains a challenge. Traditionally, the success of revascularization has been evaluated by endpoints such as wound healing and limb salvage rates [16]. However, these are very distant indicators of procedural success. Therefore, intraoperative methods for assessing the success of revascularization are needed. Currently, the evaluation of revascularization success often relies on subjective assessments, such as the observation of present wound blush in post-revascularization angiography, which is believed to correlate with an increased likelihood of better wound healing [17]. Yet, the subjectivity of such assessment limits its reliability. A new potential approach for the assessment of the procedural success could be intraoperative tissue perfusion measurement. The existing methods for perfusion measurement include hyperspectral imaging [18], 2D perfusion angiography [19], micro-oxygen sensors (MOXYs) [20], skin perfusion pressure measurement [9], transcutaneous oxymetry (TcPO2), and near-infrared spectroscopy (NIRS) [21]. However, most of these methods exhibit inconsistency and are influenced by various factors, such as temperature and vasospasm, making them unsuitable for intraoperative applications. For instance, transcutaneous oximetry, although featuring lower variability due to its proprietary heating system, poses limitations in intraoperative monitoring due to possible skin burns. In addition, transcutaneous oxymetry interferes with X-ray imaging due to the significant amount of metal alloys in the detector. Given these considerations, near-infrared spectroscopy (NIRS) emerges as a preferable choice for intraoperative tissue perfusion monitoring in this study. This selection is based on the relatively straightforward applicability of NIRS, aiming to address the limitations posed by other existing perfusion measurement methods.

The aim of this study was to evaluate and compare intraoperative oxygen saturation changes in ischemic wound regions after performing either indirect or direct angiosomal revascularization in below-the-knee arteries.

2. Materials and Methods

2.1. Study Type and Ethics

We performed a non-randomized prospective observational study at a single center, the Vilnius City Clinical Hospital. This clinical trial was reviewed and approved by the Vilnius Regional Biomedical Research Ethics Committee on the 5 December 2017, registration number 158200-17-981-482. On 2 April 2019, the study was registered in clinicaltrials.gov, registration number NCT03898869. Each participant signed an informed consent form before any study-related procedure.

2.2. Participants

All participants had to meet the inclusion and exclusion criteria depicted in Table 1. Only CLTI (Rutherford V–VI) patients with chronic total occlusion in below-the-knee arteries that were scheduled for treatment were included in this clinical trial.

Table 1. Inclusion and exclusion criteria.

Inclusion Criteria	Exclusion Criteria
All presenting PAD patients 55–95 years old	Skin diseases preventing the use of NIRS
CLTI Rutherford V–VI	Life expectancy less than 12 months
CTO below the knee	Unavoidable amputation above ankle
Planned revascularization of at least one BTK artery	Blood oxygen saturation below 85% because of any comorbidities
No need for intervention above the knee	

CLTI—critical limb-threatening ischemia; CTO—chronic total occlusion; NIRS—near-infrared spectroscopy; PAD—peripheral artery disease; BTK—below the knee.

2.3. Examination and Procedures

All patients underwent routine laboratory and clinical assessments. Ischemic wounds were evaluated using WIfI classification [22]. The Dopplex® Ankle Brachial Pressure Index Kit with an EZ8 8 MHz Probe, Huntleigh (Cardiff, Wales, UK) was used for the ankle–brachial index measurement. Either direct or indirect endovascular revascularization was carried out in all cases. The only intended revascularization technique was percutaneous transluminal angioplasty (PTA), and stenting was a bailout option in flow-limiting dissections. The operating room was equipped with the Innova 4100, GE (Boston, MA, USA). The oxygen saturation in the index finger and vital signs was registered using the B40 Patient Monitor, GE (Boston, MA, USA). Endovascular procedures were performed by a single vascular surgeon according to the local procedure protocol, with heparinization during the procedure and a prescription of dual antiplatelet therapy for 3 months after the intervention. Patient assignment to direct or indirect revascularization groups was not randomized and was performed by the operating doctor based on the vessel size, occlusion length, and outflow. If several arteries, including the angiosomal vessel, were successfully revascularized, the patients were allocated to the direct revascularization group.

Tissue oxygen saturation changes were measured intraoperatively with near-infrared spectroscopy (NIRS) using the Invos Oximeter, Somanetics/Medtronic (Dublin, Ireland). Two sensors were located on the healthy skin 2–3 cm from the ischemic wound, and one reference probe was placed on the pectoral muscle (Figure 1). During the endovascular procedure, regional oxygen saturation (rSO2) changes could be seen on the screen of the Invos Oximeter and were recorded every 6 s.

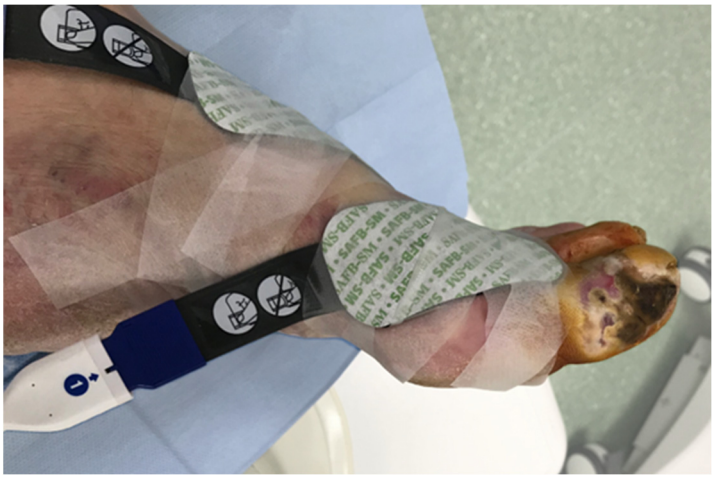

Figure 1. NIRS sensor placement near the ischemic wound.

After every procedure, the NIRS data was downloaded and post-processed using Excel v16.42, Microsoft (Redmond, WA, USA). Afterwards, the means of the first and last 50 measurements of every sensor were calculated. The formula below was used to measure the revascularization effect.

$$\text{Effect} = \left(\frac{\frac{(M_{1\alpha}+M_{2\alpha})-(M_{1\omega}+M_{2\omega})}{2} - (MR_{\alpha} - MR_{\omega})}{\frac{M_{1\alpha}+M_{2\alpha}}{2}} - 1 \right) * 100$$

where:

$M_{1\alpha}$—mean of the first 50 measurements on sensor 1 (before revascularization);
$M_{2\alpha}$—mean of the first 50 measurements on sensor 2 (before revascularization);
$M_{1\omega}$—mean of the last 50 measurements on sensor 1 (after revascularization);
$M_{2\omega}$—mean of the last 50 measurements on sensor 2 (after revascularization);
$M_{R\alpha}$—mean of the first 50 measurements on the reference sensor (before revascularization);
$M_{R\omega}$—mean of the last 50 measurements on the reference sensor (after revascularization).

2.4. Statistical Analysis

Statistical analysis was carried out using SPSS v26.0, IBM (Armonk, NY, USA). The data are presented as the mean ± SD for the continuous values, which were distributed normally, otherwise the median and interquartile range (25th and 75th percentiles) are shown (IQR). Student's *t*-test was used to assess the statistical significance of normally distributed data, the Wilcoxon signed rank test was used for continuous non-normally distributed variables, and Fisher's exact test was used for categorical variables. Differences among the samples were considered statistically significant when $p \leq 0.05$.

3. Results

This clinical trial included 30 patients with chronic limb-threatening ischemia (Rutherford V–VI) and chronic total occlusion in below-the-knee arteries. A total of 17 (57%) out of the 30 patients were male. The mean age of the patients was 74.7 ± 11.2 years. The baseline characteristics of both the direct and indirect revascularization groups are depicted in Table 2. No statistically significant difference between the groups was found regarding the baseline characteristics.

Lesions in all three angiosomes of the foot were observed in this clinical trial. The wound localization is presented in Table 3. A total of 16 patients had lesions in the anterior tibial artery angiosome, 8 patients had them in the posterior tibial artery, and 6 patients had them in the peroneal artery angiosome.

Table 2. Baseline characteristics of direct and indirect revascularization groups.

Variables	Direct Revascularization Group	Indirect Revascularization Group	*p*-Value
Age, years	72.3 ± 7.8	77.1 ± 13.7	>0.05
Male	7 (46.7%)	10 (66.7%)	>0.05
Diabetes mellitus	10 (66.7%)	6 (40%)	>0.05
End-stage renal disease	6 (40%)	4 (26.7%)	>0.05
CAD	12 (80%)	9 (60%)	>0.05

CAD—coronary artery disease. Data are presented as *n* (%) and as mean ± standard deviation.

Table 3. Ischemic wound localization according to angiosome.

	Lesions (*n* = 30)
Anterior tibial artery	16 (53.3)
Posterior tibial artery	8 (26.7)
Peroneal artery	6 (20.0)

Data are presented as *n* (%).

Every patient had angiographically verified lesions in all three below-the-knee arteries. In total, 30 endovascular below-the-knee procedures were performed, and 44 arteries were revascularized. The revascularization locations were as follows: 21 anterior tibial arteries, 10 posterior tibial arteries, 8 peroneal arteries, 2 tibioperoneal trunks, and 3 popliteal arteries. A total of 15 patients (50%) underwent direct angiosomal revascularization, and the other half of the patients underwent indirect revascularization.

The NIRS revealed a statistically significant intraoperative rSO2 increase near the wound after revascularization (paired samples *t*-test, $p = 0.001$) (Table 4).

Table 4. Intraoperative rSO2 increase in sensors 1 and 2 located near the wound.

Sensor	NIRS rSO2 before the Reperfusion	NIRS rSO2 after the Reperfusion	*p*-Value
Sensor 1	58.0 ± 12.7	66.7 ± 11.6	0.001
Sensor 2	57.6 ± 12.7	67.1 ± 14.0	<0.001

Data are presented as mean ± standard deviation.

A greater oxygen saturation increase was observed in the direct angiosomal revascularization group; however, the difference in change between the groups was not statistically significant (Mann–Whitney test, $p = 0.619$) (Table 5; Figure 2).

Table 5. Oxygenation changes in the indirect and direct angiosomal revascularization groups.

	Patients (*n* = 30)	NIRS rSO2 Change after the Revascularization
Indirect Revascularization	15 (50)	16.8 [25.7]
Direct Revascularization	15 (50)	17.9 [38.5]

Data are presented as *n* (%) and median [interquartile range, IQR].

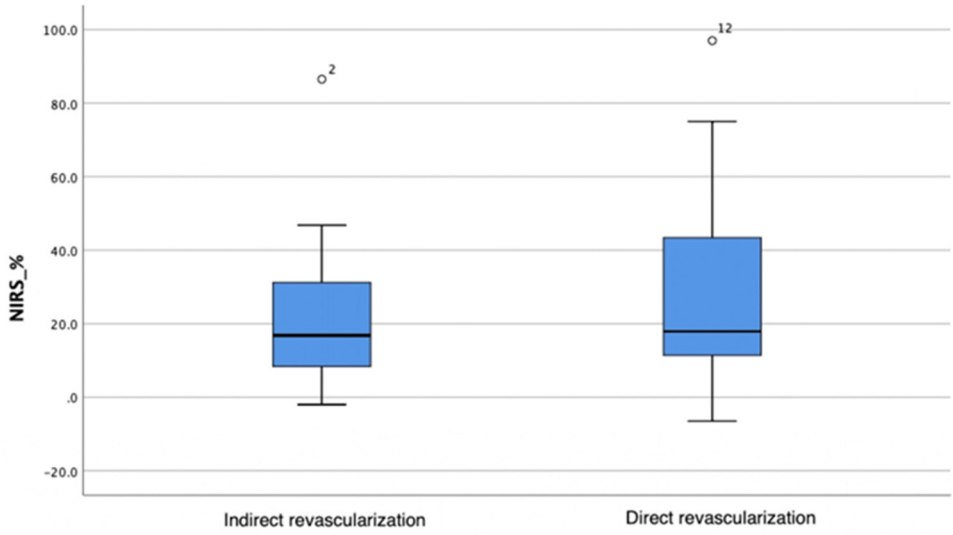

Figure 2. Oxygenation changes in the indirect and direct angiosomal revascularization groups. The horizontal bar represents the median value, while the blue box spans the interquartile range (IQR), representing the 25th to 75th percentiles. Whiskers represent minimum and maximum values. Outliers are represented separately as number 2 and number 12.

Post-Hoc Power Analysis

A post-hoc power analysis showed that, for an independent group *t*-test with a significance level of 0.05 and a power of 0.95, the required sample size was 884 subjects.

4. Discussion

Despite the fact that wound management was discussed for the first time more than 4000 years ago, the burden of chronic wounds still remains very high and accounts for around 40 million patients worldwide [23]. The prevalence of chronic wounds is notably higher among the elderly population, and with the current global demographic shift toward an increasing proportion of elderly individuals, it is anticipated that the incidence of chronic wounds will correspondingly escalate. It is also important to emphasize that especially in the elderly, chronic wounds are prone to be rather multi-etiological [2]. This complicates the assessment of the arterial component, necessitating a specific approach that incorporates the measurement of tissue perfusion in the proximity of the wound site. Since the existing methods are suboptimal, we believe that future prospects for wound evaluation and management will likely include novel methods for tissue perfusion monitoring. This study shows that, despite the limited feasibility of NIRS, under highly controlled conditions, perfusion changes in tissues near ischemic wounds could be monitored intraoperatively during both direct angiosomal and non-angiosomal revascularization procedures. These findings open new prospects for the further exploration of NIRS as a viable tool in the setting of chronic wound evaluation.

To this day, intraoperative quantitative evaluation of reperfusion remains controversial. The only validated tool for measuring perfusion in tissue is transcutaneous oximetry (TcPO2) [24]. However, the application of TcPO2 requires skin heating to 40 °C, is operator-dependent, time-consuming, and impacts X-ray imaging, which makes it not suitable for intraoperative tissue perfusion monitoring [9].

In this clinical trial, near-infrared spectroscopy (NIRS) was used to monitor tissue oxygen saturation changes in ischemic wound regions during angiosomal and non-angiosomal revascularization procedures in below-the-knee arteries. The NIRS system comprises a monitor and flexible optodes equipped with a light source and two receiving photodetectors. The basic functioning involves the generation of near-infrared (NIR) light at specific wavelengths, which are absorbed by tissue hemoglobin. This emitted NIR beam is directed into the target tissue through cutaneously attached optodes. Subsequently, the NIRS system

determines the proportion of oxygenated hemoglobin within small vessels by analyzing the amount of detected light in the photodetectors. Notably, the NIRS method, with its spectral range spanning from 700 to 1100 nm, exhibits the ability to penetrate tissue to depths several centimeters beyond the reach of visible light [25,26]. It is an easy-to-apply, non-invasive perfusion measurement method that does not interfere with X-ray imaging significantly, is not harmful to the tissue, and therefore, can be used intraoperatively for extended period of time [27]. The INVOS^{TM} regional oximeter has been validated to monitor brain perfusion during coronary artery bypass surgeries. However, the importance of this method is growing in different clinical applications [28]. Over the past 10 years, there have been 67 papers published in PubMed regarding the use of NIRS for brain perfusion monitoring during carotid endarterectomies (CEA), which implies that, due to its simplicity, NIRS is being widely adopted in this clinical setting [29,30]. Recently published clinical trials have reported the utilization of NIRS for peripheral tissue oxygen saturation monitoring in PAD patients [31–33]. Also, in 2022, Baltrunas et al. discussed the use of NIRS in the context of PAD. In their systematic review, the authors reported NIRS as a promising tissue perfusion measurement tool, particularly in diabetic patients; however, it was stated that more structured clinical data are needed in order to evaluate the effectiveness of this method in peripheral tissue oxygen saturation measurement for PAD patients [27]. Therefore, taking into account the previously carried out clinical trials as well as the existing literature, we believe that NIRS conforms well to the design of our study.

The angiosome concept was first introduced in 1987 by Ian Taylor and colleagues. There are six angiosomes in the foot, which originate from three main arteries: the anterior tibial artery, posterior tibial artery, and peroneal artery [10,33]. The angiosome concept is primarily based on the anatomy of healthy limbs and has been adopted in the field of plastic surgery. However, currently, it is being used in CLTI limbs with long-term CTO and remodeled vascular anatomy [11,12]. In their systematic review and meta-analysis, Dilaver et al. found that direct revascularization leads to better wound healing and limb salvage results [11]. On the other hand, indirect revascularization might appear beneficial when significant collateral vessels are present. Varela et al. found that post-operative outcomes after the restoration of blood flow to the ischemic area through collaterals are similar to those after direct revascularization [34]. However, in patients with diabetes and renal function impairment, collaterals are usually not well formed, making the direct technique more appropriate [15]. Despite the growing evidence supporting revascularization according to the angiosome concept, the literature comparing indirect versus direct blood flow restoration is considered to be low-quality. Moreover, it measures outcomes such as wound healing and limb salvage results, which are surrogate indicators of blood perfusion restoration, early artery recoil or later restenosis, inflammation, wound depth, and other comorbidities [11,15].

Existing studies, as well as our clinical trial, compare revascularization results between two major groups, which are based only on the angiosomal and non-angiosomal approaches (groups 1 and 2) (Table 6) [13,35–37].

Table 6. Proposed formation of subgroups.

	Optimal Vessel (a)	**Suboptimal Vessel (b)**
Angiosomal revascularization (1)	Subgroup 1a	Subgroup 1b
Non-angiosomal revascularization (2)	Subgroup 2a	Subgroup 2b

In clinical practice, there is no question that directly revascularizing the anatomically optimal vessel (subgroup 1a) (Table 6) will result in the best post-operative outcome. Also, indirect revascularization of a suboptimal vessel with impaired run-off and a small diameter (subgroup 2b) (Table 6) will lead to the poorest result. However, to this day, there is a lack

of discussion to verify which clinical scenario leads to better results: the direct angiosomal revascularization of a poor-outflow vessel (subgroup 1b) or the indirect revascularization of an optimal artery (subgroup 2a). Therefore, it can be presumed that there is a need for studies comparing the revascularization results between only the subgroups 1b and 2a, which remain controversial in clinical practice.

Even though our clinical trial is the largest trial to date investigating intraoperative angiosomal versus non-angiosomal revascularization results using NIRS, our sample was too small to divide the patients into the four previously mentioned subgroups. Future clinical trials evaluating and comparing revascularization outcomes among these less straightforward patient subgroups could potentially help gather higher-quality data on the use of the angiosome concept and would shed some light on the ongoing debates on whether direct angiosomal revascularization is superior to indirect. Also, a larger multi-center study including wound healing and limb salvage results could be beneficial.

Our study reveals only a minor difference in the rSO2 increase between the angiosomal and non-angiosomal revascularization groups (17.9% and 16.8% increases in tissue oxygen saturation, respectively). Moreover, the post-hoc power analysis showed that a very large sample of approximately 900 patients is needed to obtain a statistically significant difference between the aforementioned groups. This indicates that the difference between angiosomal and non-angiosomal revascularization is extremely small and shadowed by other variables, such as early recoil, later restenosis of treated arteries, wound depth, inflammation, etc. In addition, the existing large randomized clinical trials concerning revascularization success take into account many other factors, such as patient comorbidities or the type of debulking devices/balloons/stents used, which appear to be more influential in this clinical setting.

Being the first of this kind, this study has some limitations, such as the absence of patient randomization, which could have caused selection bias. Patient assignment to direct or indirect revascularization group was performed solely by the operating doctor based on angiographic image evaluation and the doctor's experience in this field. However, in every case, the revascularization method selection was adequate for the patient. Therefore, our results might have been affected slightly more by the operator's level of clinical expertise rather than the differences in revascularization technique.

Randomization for this type of study would need a significantly higher number of participants. However, not all occluded BTK vessels can be opened equally successfully, and there would be a huge shift among the groups for the intended treatment and actual revascularization. In this case, the sample size was too small to efficiently stratify patients regarding their angiographic baseline characteristics, MAC-SAD score, and other existing scoring systems. In this study, WIfI classification was used to assess the ischemic wounds of all participants. However, this classification itself has more possible combinations than the sample size of this study. Hence, we decided to not stratify the patients according to this classification as well.

5. Conclusions

Although this study confirmed a significant tissue oxygen saturation increase using NIRS near ischemic wounds after revascularization, only a minor difference in the oxygen saturation increase between the direct and indirect revascularization groups (17.9% and 16.8% increases in the tissue oxygen saturation, respectively) was observed. Consequently, this study indicates that the clinical significance of angiosomal revascularization is negligible and most likely concealed by the vessel diameter and outflow impact on the restenosis rate. We believe that future studies comparing the outcomes only between suboptimal angiosomal and optimal non-angiosomal revascularization subgroups are needed. Such clinical trials would guide doctors through clinical situations that, to this day, remain controversial. Furthermore, adequate intraoperative perfusion measurement methods would provide a chance to predict the success of revascularization while still being in the operating room. This would respectively lead to better patient outcomes, including more

efficient wound healing, consequently contributing to a global reduction in the economic burden imposed by chronic wounds.

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Validation of the Lithuanian Version of the Walking Impairment Questionnaire in Patients with Peripheral Arterial Disease

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Abstract: *Background and Objectives*: The Walking Impairment Questionnaire (WIQ) is a short and simple tool to measure walking impairment for patients with peripheral arterial disease requiring no special equipment or trained staff. The aim of this study was to assess the validity and reliability of the culturally adapted Lithuanian WIQ version in patients with intermittent claudication. *Materials and Methods*: In total, 40 patients with intermittent claudication and ankle–brachial index < 0.90 participated in this study. Reliability and internal consistency of the questionnaire were assessed by the intra-class correlation coefficient (ICC) and Cronbach's alpha (α), respectively. Validity was determined by correlations between the WIQ scores and a subjective test (Quality of Life 5 Dimension Questionnaire 3 Level Version (EQ-5D-3L)) and objective tests (6 min walk test (6MWT), treadmill test, and ankle–brachial index). *Results*: The test–retest reliability was assessed as excellent with an intraclass correlation coefficient of 0.90. The values of Cronbach's alpha were 0.957 (I time) and 0.948 (II time) and indicated an excellent internal consistency. Statistically significant Spearman correlations were detected between the WIQ and walking distances on the 6MWT (rho 0.514, $p < 0.001$) and treadmill test (rho 0.515, $p < 0.001$). Higher WIQ scores were associated with longer walking distances and duration. Moderate negative and low negative correlations were found between the WIQ and EQ-5D-3L scores. *Conclusions*: The Lithuanian version of culturally adapted WIQ demonstrates reliability and validity for patients with intermittent claudication, supported by two different walking tests showing statistically significant moderate Spearman correlations.

Keywords: walking impairment questionnaire; peripheral arterial disease; intermittent claudication; validation studies

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1. Introduction

Peripheral arterial disease (PAD) includes conditions that cause the obstruction of arterial blood flow, excluding the coronary and intracranial vessels, when the ankle–brachial index is lower than 0.90 [1,2]. According to systematic reviews, the prevalence of PAD was approximately 202 million individuals in 2010, and it increased to an estimated 237 million people in 2015 [3,4]. Peripheral arterial disease is associated with functional impairment, while intermittent claudication (IC) is the first and the most frequent symptom of PAD [1]. IC is classically defined as pain, including one or both of the lower extremities, that starts on walking and requires a stop to relieve pain [5]. Based on several different studies, the prevalence of IC within a general population ranges from 0.7% to 7% [6–10]. Additionally, McDermott et al. conducted a study involving patients with an ABI < 0.9 and found that 32% of individuals diagnosed with PAD exhibited typical IC symptoms [11].

The treadmill test is considered a standard method to objectively assess walking impairment for PAD patients [12]. However, treadmill testing requires specific equipment, trained staff, is time-consuming, and is inappropriate to use in primary care settings or epidemiological studies. Moreover, the treadmill test does not detect walking impairment occurring in daily life precisely, and individuals may encounter challenges walking on a treadmill due to balance disorders, frailty, or walking limitations unrelated to PAD [2]. While the majority of IC patients receive outpatient treatment, the WIQ would be a more accessible tool for assessing the severity of walking impairment.

The Walking Impairment Questionnaire (WIQ) is a short and simple questionnaire measuring ability to walk in three different subscales: walking distance, walking speed, and stair climbing [13]. The WIQ has been validated in many countries, including the USA, the Netherlands, Brazil, Spain, China, South Korea, and others [13–18]. The original WIQ version was translated into the Lithuanian language and adjusted for the metric system in a previous study [19]. The present study aimed to determine if the Lithuanian version of the culturally adapted WIQ is reliable and valid for PAD patients with intermittent claudication.

2. Materials and Methods

2.1. Participants and Study Design

A prospective study including 40 PAD patients with IC was performed. Respondents were selected from Vilnius University Hospital Santaros Clinics from 2020 February to 2023 June. The inclusion criteria were PAD with IC (grade I, categories 1–3, according to Rutherford classification [20]), ankle–brachial index (ABI) < 0.9, and age between 50 and 90. Exclusion criteria were inability to walk due to orthopedical, neurological, or other comorbidities, dependency on oxygen, and insufficient knowledge of the Lithuanian language. Baseline data, presence of comorbidities (end-stage renal disease, diabetes mellitus, previous stroke, previous myocardial infarction, hypertension), and use of statins were collected. Informed consent was obtained from every participant. This study was approved by the Vilnius Regional Bioethics Committee on 2020 February 25 Nr. 2020/2-1198-684.

2.2. Walking Impairment Questionnaire (WIQ)

The WIQ is a short, easy-to-fill-out questionnaire that was developed by Regensteiner et al. in 1990 for patients with IC to determine the severity of walking impairment in patients with PAD [21]. It contains three subscales: walking distance, walking speed, and ability to climb stairs [13].

All subscales of the WIQ were estimated by a Likert scale [22], where 0 represents inability to walk, while 4 indicates no difficulties in walking. The subscale of walking distance measures ability to walk different distances from walking indoors (around the house) to 1000 m. The walking speed subscale indicates ability to walk at different speeds from slowly walking to running or jogging. The stair climbing subscale determines ability to climb from 1 to 3 flights of stairs.

Questionnaire scoring was based on a formula presented in the original version of the WIQ [21] and was double-checked with the Dutch version of the WIQ, which was culturally adapted from imperial (feet) to metric system units [14]. The walking distance subscale score was calculated by multiplying distance in meters and the Likert score of that distance. Then, the products of each distance were summed and divided by the maximum possible score of the distance subscale. For the walking speed subscale, different speeds were given weighting multipliers (from 1.5 to 5 miles per hour, as in the original version [21]) which were multiplied by the Likert score. The products were summed and divided by the maximum score of the speed subscale. The score of the climbing stairs subscale was assessed by multiplying the number of flights of stairs by the Likert score and divided by the maximum score of the climbing stairs subscale. The results of each subscale were multiplied by 100 to obtain scores in percentages. The total score of the WIQ was calculated as a mean of three subscale scores.

The original English version of the WIQ was translated into the Lithuanian language and culturally adapted in a previous study [19]. The translation was made by two independent translators; translations were compared and then translated back into the English language to compare with the original version.

2.3. European Quality of Life 5 Dimension Questionnaire 3 Level Version (EQ-5D-3L)

EQ-5D-3L is a short quality of life questionnaire containing five questions on five different domains (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression) and the vertical visual analogue scale (VAS) [23]. Each question was assessed by the Likert scale, where 1 implies good quality of life, while 3 indicates difficulties in different situations. This scaling is opposite to the WIQ scaling system, assuming negative Spearman correlations between these two questionnaires. The vertical VAS was set from 0 to 100, where 0 means 'the worst imaginable health state' and 100 represents 'the best imaginable health state'. Spearman correlations between the VAS and WIQ were expected to be positively correlated.

2.4. 6-Minute Walk Test (6MWT)

According to the latest guidelines from the European Society for Vascular Surgery, the 6 min walk test (6MWT) should be the primary test for assessing walking capacity and evaluating the severity of intermittent claudication in PAD patients [2]. This is considered more representative of everyday ambulatory function compared to treadmill testing. Moreover, the walking distance of the 6MWT closely correlates with walking capacity outdoors in patients with IC [24]. During the test, participants were asked to walk as far as possible in 6 min, and stopping for a rest when needed was permitted. The total distance walked in 6 min was recorded.

2.5. Treadmill Test

The treadmill test is a conventional test used to establish peripheral arterial disease diagnosis and to quantify severity [12]. In addition, the maximum walking distance measured during a graded treadmill test may be deemed the most trustworthy parameter for the treadmill [2]. In our study, the test started with a 0% incline and was increased by 2% every 2 min. The speed of the treadmill was constant and equal to 3.2 km/h. The test was terminated once the patient experienced IC. Walking duration, maximum walking distance, and reached incline angle were recorded.

2.6. Ankle–Brachial Index (ABI)

The ABI is a noninvasive and easily accessible method for diagnosing and estimating the severity of lower limb PAD [2]. The ABI is a ratio between the systolic blood pressures of the ankle and the upper extremity. An ABI lower than 0.9 indicates PAD with serious stenosis [25]. In our study, the ABI was measured with the Hokanson MD35 model (Bellevue, WA, USA) separately for both sides (left and right). The lower ABI was chosen for the analysis.

2.7. Validation Process

Reliability of the Lithuanian version of the WIQ was determined by internal consistency and test–retest reliability. Internal consistency determines the degree to which the test items jointly measure the same construct and was calculated in Cronbach's alpha (α) [26]. Test–retest reliability was estimated by completing the WIQ twice and assessed by the intraclass correlation coefficient (ICC) [27]. The period between the first and second tests was two weeks. This duration was considered to be long enough for the patient to not remember their answers but short enough not to have a significant treatment effect.

The validity of the WIQ was measured by Spearman correlations with functional tests (6MWT and treadmill tests) and a subjective test (EQ-5D-3L). We have also assessed the Spearman correlations between the WIQ and ABI. Spearman correlations were assessed

between each item and WIQ subscores, as well as the WIQ total score. In addition, we have conducted a power study.

2.8. Statistical Analysis

Demographic data and the results of walking tests, questionnaires, and the ABI were given as a mean and standard deviation (SD) for normal distribution based on the Shapiro–Wilk test [28]. Otherwise, the data were illustrated using a median and interquartile range (IQR). Comorbidities were presented as the number and the percentage of participants.

The ICC was measured to determine test–retest reliability corresponding to ICC (3, B) by the conventions of Shrout and Fleiss [27]. The confidence interval was set to 95%. ICC < 0.50 was determined to be poor, 0.50 ≤ ICC < 0.75—moderate, 0.75 ≤ ICC < 0.90—good, and ICC ≥ 0.90—excellent [29]. Internal consistency was assessed by calculating Cronbach's alpha(α). Based on George and Mallery's rule of thumb, α ≥ 0.90 was determined as excellent, 0.80 ≤ α < 0.90—good, 0.70 ≤ α < 0.80—acceptable, 0.60 ≤ α < 0.70—questionable, 0.50 ≤ α < 0.60—poor, and <0.50—unacceptable internal consistency [30]. Correlations between the WIQ and 6MWT, treadmill test, ED-5D-3L, and ABI were assessed using Spearman correlation coefficients. Spearman correlations (Spearman's rho) ≥ 0.90 were interpreted as very high, 0.70 ≤ rho < 0.90—high, 0.50 ≤ rho < 0.70—moderate, and 0.30 ≤ rho < 0.50—low, while correlations with rho < 0.30 were determined to be insignificant [31]. The statistical power analysis was conducted to assess the probability of rejecting the null hypothesis when it is false [32].

Statistical analysis was performed with JASP version 0.17.3 for Windows and G Power version 3.19.6.

3. Results

3.1. Baseline Data

In total, 40 PAD patients with IC were enrolled in this study. One patient was excluded after not arriving for the functional (6MWT and Treadmill) tests. A total of 84.6% of the participants were men, and the mean age was 68.8 (SD 8.9). Regarding the occurrence of comorbidities, 57.5% of the participants had elevated arterial blood pressure, 35.0% were prescribed statins, 25.0% had a history of myocardial infarction, 20.0% were diagnosed with diabetes mellitus, 12.5% had a prior history of stroke, 12.5% were suffering from end-stage renal disease, and 10.0% were afflicted by chronic obstructive pulmonary disease.

The mean score of the WIQ total score was 48.8 (SD 20.8), and the mean ABI was 0.59 (SD 0.12). The median walking distances during the 6MWT and treadmill test were 390.0 m (IQR 108.0) and 80.0 m (IQR 60.0), respectively. The remaining results of the objective (6MWT, treadmill test) and subjective (EQ-5D-3L) tests are shown in Table 1.

Table 1. Baseline data.

Tests	Mean (±SD)	Median (±IQR)
WIQ total	48.8 (±20.8)	
WIQ distance		26.0 (±42.0)
WIQ speed	40.5 (±23.8)	
WIQ stair climbing		68.8 (±26.0)
6MWT distance		390.0 (±108.0)
Treadmill distance		80.0 (±60.0)
Treadmill duration		104.0 (±80.0)
Treadmill incline angle		0.0 (±2.0)
ABI	0.59 (±0.12)	
EQ-5D-3L Total		8.0 (±2.0)
EQ-5D-3L Mobility		2.0 (±1.0)
EQ-5D-3L Self-care		1.0 (±1.0)
EQ-5D-3L Usual activities		1.5 (±1.0)
EQ-5D-3L Pain/discomfort		2.0 (±0.0)
EQ-5D-3L Anxiety/depression		2.0 (±1.0)
VAS	55.0 (±14.1)	

3.2. Test–Retest Reliability and Internal Consistency

The ICC for the test–retest reliability for the total WIQ score was 0.90 (excellent). The ICCs for the walking distance, walking speed, and stair climbing subscales were 0.91 (excellent), 0.84 (good), and 0.80 (good), respectively (Table 2). The internal consistency, represented by Cronbach's alpha (α), for the total WIQ score was assessed as excellent, with values equal to 0.96 (I time) and 0.95 (II time). Internal consistency values of each WIQ subscale are presented in Table 3.

Table 2. Test–retest reliability (ICC).

WIQ	Time I Mean (SD)	Time II Mean (SD)	Change of Scores Mean (SD)	ICC	95% Confidence Interval
Total	47.37 (21.82)	50.17 (20.76)	−2.80 (9.52)	0.90	0.82–0.95
Distance	34.09 (28.37)	33.65 (28.31)	0.43 (12.45)	0.91	0.83–0.95
Speed	38.57 (25.39)	42.50 (24.27)	−3.93 (13.94)	0.84	0.72–0.91
Stair climbing	69.44 (22.36)	74.36 (19.63)	−4.92 (13.48)	0.80	0.64–0.89

Table 3. Internal consistency (Cronbach's alpha (α)).

WIQ	Time I Cronbach's Alpha(α)	95% Confidence Interval (I)	Time II Cronbach's Alpha(α)	95% Confidence Interval (II)
Total	0.96	0.93–0.97	0.95	0.92–0.97
Distance	0.95	0.92–0.97	0.94	0.91–0.97
Speed	0.93	0.88–0.96	0.89	0.82–0.94
Stair climbing	0.87	0.78–0.93	0.81	0.70–0.89

3.3. Validity

Correlations between the WIQ and walking distance during two functional tests (6MWT and treadmill test) were moderate, with Spearman correlation coefficients of 0.51 and 0.52 (both $p < 0.001$) and power values of 0.93 and 0.94, respectively. Total WIQ scores were plotted against the distances of the 6MWT and treadmill test in Figure 1. Furthermore, higher WIQ scores were associated with longer walking distances and duration (Table 4).

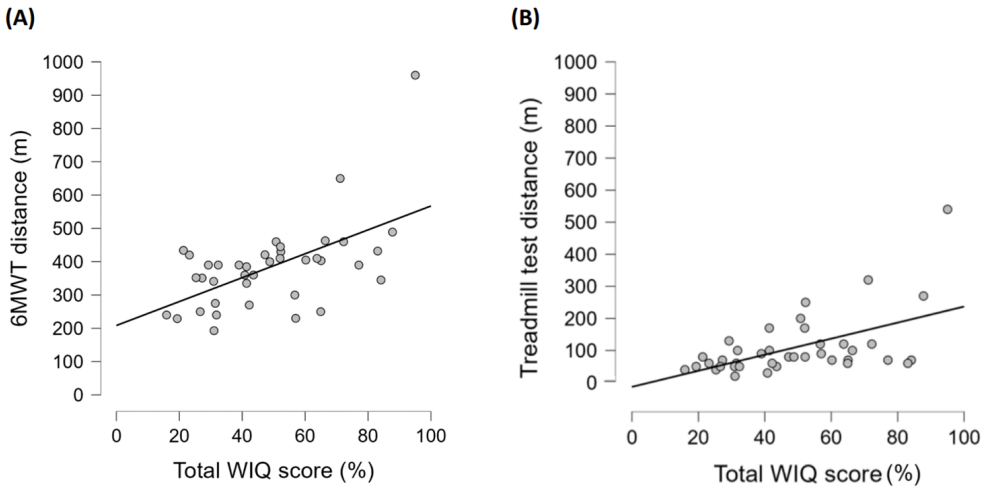

Figure 1. (**A**) The total WIQ score plotted against the distance of the 6MWT; (**B**) the total WIQ score plotted against the distance of the treadmill test.

Table 4. Quartiles of the Lithuanian version of WIQ scores compared with walking distances.

WIQ Total Score in Quartiles	6MWT Distance (m)–Mean (SD)	Treadmill Distance (m)–Mean (SD)	Treadmill Duration (s)–Mean (SD)
0.0–31.2	320.0 (85.7)	59.0 (30.0)	88.4 (40.5)
31.2–47.2	342.6 (61.0)	79.0 (39.6)	120.2 (46.5)
47.2–64.4	387.8 (74.4)	131.1 (62.5)	165.9 (77.6)
64.4–100.0	484.2 (196.5)	168.0 (160.2)	223.0 (198.9)

There was a low positive correlation between the total WIQ score and walking duration during the treadmill test (rho = 0.45, p = 0.004). However, no significant correlation was observed between the total WIQ score and the incline angle reached during the treadmill test.

Correlations between the WIQ and EQ-5D-3L (subjective test) were estimated to fall between moderate negative and low negative correlations. Spearman correlation coefficients between the total WIQ score and EQ-5D-3L domains representing anxiety/depression (rho = −0.61, $p < 0.001$), usual activities (rho = −0.51, $p < 0.001$), and mobility (rho = −0.48, p = 0.002) were higher than self-care (rho = −0.39, p = 0.014) and pain/discomfort (rho = −0.34, p = 0.032). A low positive correlation (rho = 0.49, p = 0.001) was observed between the WIQ and VAS. The remaining correlations between the WIQ and EQ-5D-3L are presented in Table 5.

Table 5. Spearman correlation coefficients between the WIQ and EQ-5D-3L.

	WIQ Total	WIQ Distance	WIQ Speed	WIQ Stair Climbing
EQ-5D-3L Total	−0.67 ***	−0.64 ***	−0.69 ***	−0.43 **
EQ-5D-3L Mobility	−0.48 **	−0.46 **	−0.43 **	−0.29
EQ-5D-3L Self-care	−0.39 *	−0.34 *	−0.52 ***	−0.22
EQ-5D-3L Usual activities	−0.51 ***	−0.47 **	−0.56 ***	−0.35 *
EQ-5D-3L Pain/discomfort	−0.34 *	−0.32 *	−0.30	−0.20
EQ-5D-3L Anxiety/depression	−0.61 ***	−0.59 ***	−0.57 ***	−0.41 **

* $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$.

There were no significant correlations between the ABI and total WIQ score, walking speed subscale, or stair climbing subscale. A significant correlation was observed between the ABI and WIQ walking distance subscale, and this was determined as a low positive correlation (rho = 0.38, p = 0.018).

Power analysis was conducted due to the small sample size. When the Spearman correlation coefficient (rho) is 0.5, a sample size of 29 is deemed sufficient. In contrast, when the correlation coefficient is 0.3, a larger sample size of 84 is necessary. These calculations are made under the assumption of rejecting the null hypothesis, which posits that there is no correlation. Furthermore, these computations were performed with a target statistical power of 0.8, and α error was set at 0.05.

4. Discussion

The Lithuanian version of the WIQ showed good test–retest reliability, internal consistency, and correlations with functional tests (6MWT and treadmill). The Dutch version of the WIQ was the first version adapted for the metric system [14]. The main limitation of that study was that the treadmill test may not reflect the actual walking distance in daily life. Therefore, we included both the treadmill test and 6MWT, which illustrate daily life walking more closely [33]. Relationships between the WIQ and walking distances in two different tests (6MWT and Treadmill) were significant with moderate Spearman correlation coefficients. Finally, the positive correlation between walking distances and the WIQ, as illustrated by quartile scores, shows that the WIQ could help to differentiate patients by the severity of their walking impairment.

Despite the objective measuring of the ABI, no or low significant correlation between the ABI and WIQ was expected based on previous WIQ validation studies in other countries [13,17,34]. Furthermore, we found no significant correlations between the ABI and walking distances on functional tests (6MWT (rho = 0.23, p = 0.165) and the treadmill test (rho = 0.17, p = 0.303)). A recent meta-analysis of the toe–brachial index (TBI) and ankle–brachial index (ABI) in the diagnosis of PAD in lower extremities suggested a large heterogeneity in sensitivity for the ABI, better sensitivity of the TBI (82% vs. 52%), and better specificity of the ABI (77% vs. 94%) [35]. These observations show that the WIQ might be a more reliable tool to determine walking impairment severity in patients with PAD than a classical ABI test. We also indicate the importance of further studies to test the reliability of the ABI for determining the severity of walking impairment.

The clinical significance of the WIQ validation has several aspects. Although it may not be the main diagnostic test for PAD with IC, the WIQ could evolve into a crucial tool for assessing the severity of walking impairment, as indicated by quartile scores. While the PAD is closely related to other cardiovascular diseases, such as coronary artery disease, carotid artery disease, and renal artery disease, the early determination of PAD severity could have a significant impact on outcomes. Moreover, the WIQ is a fast, easy to complete method requiring no specialized tools or trained staff. Finally, the validation of the Lithuanian version of the WIQ provides a good tool for further studies involving PAD patients.

There were several limitations of this study. Firstly, the sample size of this study was quite small and was not designed to represent all social backgrounds. In addition, not assessing the mental abilities of the participants may have affected the WIQ results of patients with dementia, post-stroke complications, or other cognitive dysfunction symptoms. Five questions of the EQ-5D-3L questionnaire might not give sufficient information about quality of life. As questionnaires give subjective results, a more comprehensive quality of life questionnaire (such as Medical Outcome Study Questionnaire Short Form 36 (SF-36) or Lifestyle and Clinical Survey) should be chosen [14,15,34]. The last limitation was the cultural adaptation of the WIQ. Standard size living blocks are not common in Lithuanian architecture, so questions in the WIQ distance subscale were only presented in meters, which could have made it difficult for the subjects to evaluate distances properly. Moreover, the lowest correlation observed between the WIQ stair climbing subscale and other tests could have been affected by the term 'flight of stairs', which is not widespread in the Lithuanian language. It would have been more accurate to add a number of how many stairs to each question of the stair climbing subscale, as occurred in the study of the validation of the Brazilian version of the WIQ [15].

Based on the lowest correlations between the WIQ stair climbing subscale and other results, further studies are needed to assess the relationship between the WIQ and functional test directly associated with stair climbing. Furthermore, a wide epidemiological study is necessary to determine whether the WIQ is capable of indicating the severity of walking impairment for PAD patients more precisely than the classical ABI test. Finally, based on the latest guidelines from the European Society for Vascular Surgery, further studies are needed to determine whether the WIQ is capable of differentiating PAD patients from outpatients, minimally invasive or open surgical treatment, as well as assessing the treatment of IC patients [2].

5. Conclusions

Reliability was assessed with good to excellent test–retest reliability and excellent internal consistency. The validation process involved the inclusion of two different walking tests, and statistically significant moderate correlations were observed with both assessments. Additionally, correlations between the WIQ and EQ-5D-3L were significant, ranging from moderate negative to low negative correlations. To conclude, the Lithuanian version of the culturally adapted WIQ is a reliable, valid, and clinically significant tool for quickly

assessing the severity of walking impairment in PAD patients with IC without the need for trained staff and specialized expensive tools.

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PEDIATRIJA

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Vilniaus universiteto Vaikų ligų klinika
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Vaikų ir paauglių krūtų problemos

BREAST PROBLEMS IN CHILDREN AND ADOLESCENTS

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Raktažodžiai: vaikų ir paauglių krūtų vystymosi sutrikimai, mastitas, vaikų krūties vėžys, ginekomastija.

Santrauka

Vienas svarbiausių brendimo požymių paauglystėje yra krūtų vystymasis. Dauguma krūtų pakitimų vaikystėje ir paauglystėje būna gerybiniai, tačiau visais atvejais jie kelia nepilnavertiškumą jausmą ir susirūpinimą tiek pacientui, tiek jų artimiesiems. Šiame straipsnyje apžvelgiamos pagrindinės vaikų ir paauglių krūtų problemos, tokios kaip krūtų infekcijos, dariniai ir ginekomastija.

Krūtų vystymasis

Krūtys pradeda formuotis 4 nėštumo savaitę, kai [illegible]no ventraliniame paviršiuje nuo pažastie[illegible]kšnies išsidėsto poriniai ektoderminiai sustorėjimai, vadinami krūties gūbriais arba pieno linijomis. Vėliau vystosi tik virš 4 tarpšonkaulinio tarpo esantys gūbriai, o likusi dalis atrofuojasi. Augant ir vystantis vaisiui dėl steroidinių hormonų poveikio krūtų pumpurai didėja, atsiranda liaukų elementai. Riebalinis audinys ir pieno latakai auga veikiant estrogenams, o progesteronas stimuliuoja liaukų skiltelių ir alveolių augimą [1].

Telarchė paprastai prasideda 8–13 metų amžiaus mergaitėms (vidutinis amžius – 10,3 metų) [2, 3]. Krūties pumpuras yra pirmasis brendimo požymis, o visiškai krūtys susiformuoja per vidutiniškai 4,2 metų [4]. Paauglių krūtų vystymasis apibūdinamas 1969 metais Tannerio aprašytomis stadijomis (*1 pav.*) [5].

Krūtų apžiūra

Vaikų ir paauglių krūtis profilaktiškai turėtų apžiūrėti šeimos gydytojas ar pediatras kas 1 metus [6, 7]:

- apžiūrint **naujagimius**, įvertinamas krūtų dydis, spenelių pozicija, skaičius ir jų išskyros [7]. Krūtų asimetrija ir pieną primenančios išskyros naujagimystėje gali būti normalus radinys tiek mergaitėms, tiek berniukams dėl stimuliuojančiai veikiančių mamos hormonų;
- apžiūrint **vaiką iki brendimo pradžios**, palpuojama krūtinės ląstos siena dėl papildomų

Straipsnis recenzuotas