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Ocena stężenia biomarkerów, parametrów elektrokardiograficznych i echokardiograficznych u dzieci z kardiomiopatią

Rozprawa na stopień doktora nauk medycznych i nauk o zdrowiu w dyscyplinie nauki medyczne

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SPIS TREŚCI

1. WYKAZ STOSOWANYCH SKRÓTÓW

DCM – (*dilated cardiomyopathy)* kardiomiopatia rozstrzeniowa
EKG – 12-odprowadzeniowe badanie elektrokardiograficzne
ESC – (*European Society of Cardiology)* – Europejskie Towarzystwo Kardiologiczne
HCM – (*hypertrophic cardiomyopathy)* – kardiomiopatia przerostowa
ICD – (*implantable cardioverter defibrillator)* – wszczepialny kardiowerter defibrylator
LASI – (*left atrial stiffness index)* – indeks sztywności lewego przedsionka
LASr – (*left atrial strain during reservoir phase)* –odkształcenie (*strain*) lewego przedsionka w fazie rezerwuarowej (napełniania)
LASct – (*left atrial strain during contraction phase)* –odkształcenie (*strain*) lewego przedsionka w fazie jego skurczu
LAScd – (*left atrial strain during conduit phase)* – odkształcenie (*strain*) lewego przedsionka w fazie konduitowej (zwanej również przewodową, tj. przed skurczem przedsionka)
LVAD – (*left ventricle assist device)* – urządzenie wspomagające lewą komorę serca
LVEDd – (*left ventricular end-diastolic diameter)* – wymiar końcowo-rozkurczowy lewej komory
LVEF – (*left ventricular ejection fraction)* – frakcja wyrzutowa lewej komory
LV GLS – (*left ventricular global longitudinal strain)* – całkowite podłużne odkształcenie (*strain*) lewej komory
LVNC – (*left ventricular non-compaction)* – niescalenie mięśnia lewej komory
NT-proBNP – (*N-terminal pro-B-type natriuretic peptide)* – fragment końcowy peptydu natriuretycznego typu B
NZK – nagły zgon sercowy
strain – odkształcenie
STE – *(speckle tracking echocardiography)* – echokardiografia metodą śledzenia markerów akustycznych
VT – (*ventricular tachycardia)* – częstoskurcz komorowy

2. STRESZCZENIE

Kardiomiopatie to pierwotne choroby mięśnia sercowego charakteryzujące się jego nieprawidłową budową i funkcją. Jest to rzadka grupa chorób w populacji pediatrycznej, ale związana z istotnym ryzykiem zgonu z przyczyn sercowych. W populacji dziecięcej najczęściej występują: kardiomiopatia rozstrzeniowa (DCM – *dilated cardiomiopathy),* przerostowa (HCM – *hypertrophic cardiomyopathy)* oraz niescalenie mięśnia lewej komory (LVNC - *left ventricular non-compaction)*.

Celem rozprawy doktorskiej, składającej się z cyklu 3 publikacji, była ocena czynników ryzyka niekorzystnego przebiegu DCM, HCM i LVNC w populacji pediatrycznej. Badania miały na celu podsumowanie dotychczas opisanych w literaturze parametrów oraz poszukiwanie nowych czynników związanych z niekorzystnym rokowaniem. W praktyce klinicznej pomocne są narzędzia wyróżniające pacjentów wymagających największej uwagi klinicznej od tych z łagodnym fenotypem. Jednak, dostępne dane dotyczące szacowania ryzyka u dzieci z kardiomiopatią wydają się być ciągle niewystarczające. W związku z tym przeprowadzono prospektywne badanie obserwacyjne dzieci z DCM, HCM i LVNC. Wszystkim pacjentom w momencie włączenia do badania wykonano 12-odprowadzeniowy zapis EKG, 24-godzinne monitorowanie Holter EKG, badanie echokardiograficzne oraz oznaczono stężenie biomarkerów sercowych w surowicy. Wyniki badań dzieci z kardiomiopatią porównano z wynikami zdrowych dzieci z grupy kontrolnej, które były dobrane pod względem wieku oraz płci. Przeprowadzone badania miały na celu: poszukiwanie nowych parametrów elektrokardiograficznych i echokardiograficznych związanych z niekorzystnym rokowaniem oraz czynników pozwalających odróżnić dzieci z kardiomiopatią od zdrowych.

W pierwszej publikacji opisano wyniki przeglądu systematycznego badań dotyczących niescalenia mięśnia lewej komory w populacji pediatrycznej i parametrów elektrokardiograficznych, echokardiograficznych, rezonansu magnetycznego serca oraz genetycznych związanych z gorszym rokowaniem. Omówiono również związek pomiędzy obecnością wrodzonej wady serca i współwystępowaniem innego typu kardiomiopatii a przebiegiem choroby u dzieci z LVNC. Poprzez przeprowadzenie przeglądu systematycznego uporządkowano dotychczasową wiedzę dotyczącą niescalenia mięśnia lewej komory u dzieci, omówiono różnorodne stosowane kryteria diagnostyczne oraz wyróżniono czynniki związane z niekorzystnym przebiegiem choroby.

W drugiej publikacji przeprowadzono analizę zapisów elektrokardiograficznych 42 dzieci z kardiomiopatią (19 z DCM, 17 z HCM, 6 z LVNC) oraz 19 dzieci z grupy kontrolnej. Wartość kąta QRS-T u dzieci z kardiomiopatią w porównaniu do wartości uzyskanych u dzieci z grupy kontrolnej była istotnie wyższa (w grupie DCM 75º vs. 41º p=0.007; w grupie HCM

100º vs. 41º p<0.001, w grupie LVNC 64º vs. 41º, p=0.03). Wykazano również, że wartość kąta QRS-T>120º w zapisie EKG wiązała się z istotnie większym ryzykiem zgonu wśród dzieci z kardiomiopatią. Ponadto, stwierdzono związek pomiędzy nieprawidłowymi stężeniami NT-proBNP (*N-terminal pro-B-type natriuretic peptide* – fragment końcowy peptydu natriuretycznego typu B) oraz troponiny I w surowicy krwi, a gorszą przeżywalnością u dzieci z kardiomiopatią.

W trzeciej publikacji przeanalizowano wyniki badania echokardiograficznego 56 dzieci z kardiomiopatią (28 z DCM, 21 z HCM, 7 z LVNC) oraz 28 dzieci z grupy kontrolnej. Dowiedziono, że wartość odkształcenia (*strain*) ściany lewego przedsionka w fazie rezerwuarowej (LASr) <20%, w fazie konduitowej (LAScd) ≥ -12% oraz wartość indeksu sztywności lewego przedsionka (LASI) ≥0,26 są związane z gorszą przeżywalnością u dzieci z kardiomiopatią. Model klasyfikacji lasu losowego wykazał wyższość LASr, LAScd oraz LASI nad konwencjonalnymi parametrami służącymi do oceny funkcji rozkurczowej lewej komory serca w przewidywaniu niekorzystnego punktu końcowego wśród dzieci z kardiomiopatią. Przeprowadzone badania wykazały również, że wartości LASr, LAScd, LASct oraz LASI różniły się statystycznie istotnie u pacjentów z kardiomiopatią o łagodnym fenotypie od wartości uzyskanych u dzieci z grupy kontrolnej (w grupie DCM odpowiednio: LASr 30,10% (IQR 24,20; 41,40) vs. 50,65% (IQR 44,90; 56,10) p<0,001, LAScd -25,49% ±10,99% vs. -38,77% ±10,34% p<0,001, LASct -6,21% ± 8,91% vs. -13,77% ± 4,25% p<0,001, LASI 0,22 (IQR 0,16;0,42) vs. 0,12 (IQR 0,10;0,14) p<0,001; w grupie HCM odpowiednio: LASr 37,40% (IQR 32,10;39,70) vs. 50,65% (IQR 44,90;56,10) p<0,001, LAScd -23,75% (IQR -30,20;-21,20) vs. -36,9% (IQR -44,15;-31,60) p<0,001, LASct -10,05% (IQR -12,50;-7,70) vs. -14,25% (IQR -17,50;-10,65) p=0,03, LASI 0,2 (IQR 0,18;0,27) vs. 0,12 (IQR 0,10;0,14) p<0,001).

Podsumowując, na podstawie przeprowadzonych badań ustalono nowe obiecujące czynniki ryzyka niekorzystnego przebiegu choroby u dzieci z kardiomiopatią rozstrzeniową, przerostową oraz niescaleniem mięśnia lewej komory. Ponadto, przedstawiono parametry, które mogą być pomocne w zidentyfikowaniu dzieci z chorobą o łagodniejszym fenotypie i wczesnym stadium kardiomiopatii.

3. SUMMARY

Cardiomyopathies are primary diseases of the heart muscle characterized by its abnormal structure and function. This is a rare group of pathologies in the pediatric population, but it is associated with significant risk of cardiac death. In the pediatric population the most common cardiomyopathies are: dilated cardiomyopathy (DCM), hypertrophic cardiomyopathy (HCM) and left ventricular non-compaction (LVNC).

The aim of this dissertation, which consists of a cycle of 3 published articles, was to assess the risk factors associated with unfavorable course of DCM, HCM and LVNC in the pediatric population. The study aimed at reviewing factors outlined in the literature and searching for new factors associated with worse prognosis. In clinical practice, tools helpful in distinguishing patients requiring most clinical attention from those with a benign phenotype are necessary. However, available data on risk assessment in children with cardiomyopathies is still insufficient. Therefore, a prospective observational study was conducted in children with DCM, HCM and LVNC. At the time of enrollment in the study all patients underwent: 12-lead ECG recordings, 24-hour Holter ECG monitoring, echocardiography and blood tests in order to obtain serum concentration of cardiac biomarkers. The results of children with cardiomyopathies were compared with results obtained in healthy, age and sex matched children. The conducted study aimed at: searching for new electrocardiographic and echocardiographic factors associated with unfavorable outcomes as well as factors helpful in distinguishing patients with cardiomyopathies from healthy ones.

The first paper presents a systematic review of the literature regarding left ventricular noncompaction in the pediatric population and electrocardiographic, echocardiographic, cardiac magnetic resonance imaging and genetic parameters associated with worse prognosis. The relationship between the presence of congenital heart defect or the co-existence of other types of cardiomyopathy and the course of the disease in children with LVNC has also been described. Through this systematic review, current knowledge regarding pediatric LVNC was summarized, different diagnostic criteria were discussed, and factors associated with unfavorable outcomes were outlined.

The second paper focused on electrocardiographic findings in 42 children with cardiomyopathies (19 with DCM, 17 with HCM, 6 with LVNC) and 19 in the control group. It was found that, the value of the QRS-T angle differed significantly between children with the disease and the control group (in the DCM group 75º vs. 41º p=0.007; in the HCM group 100º vs. 41º p<0.001, in the LVNC group 64º vs. 41º, p=0.03). Moreover, QRS-T angle > 120º was associated with a significantly higher risk of death among children with cardiomyopathies. This study also demonstrated the association between abnormal NT-proBNP (*N-terminal pro-B-type*

natriuretic peptide) and troponin I serum concentrations with poorer survival in children with cardiomyopathies.

In the third paper echocardiographic parameters were analyzed in 56 children with cardiomyopathies (28 with DCM, 21 with HCM, 7 with LVNC) and 28 in the control group. It was proven, that: left atrial strain in the reservoir phase (LASr) <20%, left atrial strain in the conduit phase (LAScd) ≥ -12% and left atrial stiffness index (LASI) ≥0.26 were all associated with reduced survival. On the random forest classification model LASr, LAScd and LASI were superior to conventional parameters which are used for left ventricular diastolic function assessment in terms of anticipation of unfavorable outcome. Moreover, it was shown that LASr, LAScd, LASct and LASI values differed significantly between patients with cardiomyopathy with mild phenotype and healthy children (respectively in the DCM group: LASr 30.10% (IQR 24.20; 41.40) vs. 50.65% (IQR 44.90; 56.10) p<0.001, LAScd -25.49% ± 10.99% vs. -38.77% ± 10.34 p<0.001, LASct -6.21% ± 8.91% vs. -13.77% ± 4.25 p<0.001, LASI 0.22 (IQR 0.16;0.42) vs. 0.12 (IQR 0.10;0.14) p<0.001; in the HCM group: LASr 37.40% (IQR 32.10; 39.70) vs. 50.65% (IQR 44.90;56.10) p<0.001, LAScd -23.75% (IQR -30.20;-21.20) vs. -36.9% (IQR -44.15;-31.60) p<0.001, LASct -10.05% (IQR -12.50;-7.70) vs. -14.25% (IQR -17.50;-10.65) p=0.03, LASI 0.2 (IQR 0.18;0.27) vs. 0.12 (IQR 0.10;0.14) p<0,001).

In conclusion, based on the performed studies, new promising risk factors associated with unfavorable course of DCM, HCM and LVNC in children were discovered. Moreover, parameters helpful in identifying children with a mild phenotype and early-stages of cardiomyopathy were outlined.

4. WSTĘP

Kardiomiopatie to grupa chorób charakteryzująca się pierwotnym zaburzeniem budowy oraz funkcji mięśnia sercowego. Według wytycznych Europejskiego Towarzystwa Kardiologicznego (ESC) z 2023r. stosuje się podział na: kardiomiopatię rozstrzeniową (*dilated cardiomyopathy* - DCM), przerostową (*hypertrophic cardiomyopathy* - HCM), nierostrzeniową lewej komory, arytmogenną prawej komory oraz restrykcyjną [1]. Ponadto, wyróżniane są również inne cechy fenotypowe takie jak: niescalenie mięśnia lewej komory (*left ventricular non-compaction* - LVNC) oraz zespół Takotsubo [1].

W populacji dziecięcej kardiomiopatie to stosunkowo rzadka grupa chorób, jednak związana z istotnym ryzykiem nagłego zgonu sercowego czy kwalifikacji do przeszczepu serca [2,3]. Wśród dzieci najczęściej występuje DCM definiowana jako pierwotne powiększenie lewej komory powyżej 2 odchyleń standardowych w stosunku do wzrostu i masy ciała (*z*-score >2) wraz z upośledzeniem jej funkcji skurczowej <55% w badaniu echokardiograficznym lub innym badaniu obrazowym [4]. Jej częstość występowania szacowana jest na 0,6-0,7/100 000/ rok. Etiologia dziecięcej DCM jest najczęściej idiopatyczna lub genetycznie uwarunkowana, rzadziej występuje wtórnie do chorób mitochondrialnych, nerwowo-mięśniowych czy wrodzonych wad metabolizmu. Choroba ma często charakter postępujący i może prowadzić do schyłkowej niewydolności serca oraz wystąpienia groźnych zaburzeń rytmu takich jak częstoskurcze komorowe (*ventricular tachycardia* - VT). Szacuje się, że około 50% pacjentów z idiopatyczną DCM umiera lub wymaga przeszczepienia serca w ciągu 5 lat [4].

W grupie pacjentów pediatrycznych z DCM podejmowano próby wykazania parametrów pomocnych w szacowaniu ryzyka niekorzystnego przebiegu choroby definiowanego jako: zgon, przeszczep serca czy zagrażająca arytmia komorowa. Dotychczas wyróżniono kilka czynników ryzyka: nieprawidłowe wzrastanie, objawy kliniczne, podwyższone wartości biomarkera sercowego NT-proBNP (*N-terminal pro-B-type natriuretic peptide* – N-końcowy fragment peptydu natriuretycznego typu B), stopień dysfunkcji i powiększenia lewej komory (wymiar końcowo-rozkurczowy lewej komory - *left ventricular end-diastolic dimension* (LVEDd), frakcja wyrzutowa lewej komory – *left ventricular ejection fraction* (LVEF), całkowite podłużne odkształcenie (*strain*) lewej komory - *left ventricular global longitudinal strain* (LV GLS)) czy nieprawidłowości w zapisie elektrokardiograficznym dotyczące zarówno załamków P, zespołów QRS jak i odcinka QT [3,5,6]. W populacji pediatrycznej brakuje jednak danych dotyczących roli odkształcenia (*strain*) lewego przedsionka w badaniu echokardiograficznym czy parametru ilościowo oceniającego nieprawidłowości w zapisie EKG.

Kardiomiopatia przerostowa to drugi najczęstszy typ kardiomiopatii dziecięcych, a częstość jej występowania szacowana jest na około 0,47/100 000/rok [7]. Ten typ kardiomiopatii rozpoznawany jest, gdy grubość mięśnia ściany lewej komory przekracza 2 odchylenia standardowe w stosunku do wzrostu i masy ciała pacjenta (*z*-score>2) oraz wykluczone są wtórne przyczyny przerostu (np. nadciśnienie tętnicze, koarktacja aorty, stenoza aortalna) [1]. Etiologia kardiomiopatii przerostowej w populacji dziecięcej jest najczęściej sarkomerowa lub idiopatyczna (u około 60% pacjentów), w pozostałych przypadkach związana jest z RAS-opatiami (zespołami nerwowo-sercowo-twarzowo-skórnymi związanymi z mutacjami w szlaku RAS-MAPK tzw. syndromiczne HCM), wrodzonymi wadami metabolizmu czy chorobami nerwowo-mięśniowymi [2]. W grubym, przerośniętym mięśniu sercowym mogą pojawiać się ogniska włóknienia predysponujące pacjentów do występowania częstoskurczów komorowych (VT) i zwiększonego ryzyka nagłego zgonu sercowego (NZK). U dzieci ryzyko to szacowane jest na około 1.5%/rok [8].

W 2019 i 2020 roku pojawiły się dwie skale pomocne w szacowaniu ryzyka nagłego zgonu sercowego u dzieci z kardiomiopatią przerostową (skala HCM Risk-Kids oraz PRIMACY) [9,10]. W obu skalach brane są pod uwagę następujące parametry: utraty przytomności, nieutrwalone częstoskurcze komorowe oraz niektóre parametry echokardiograficzne (maksymalna grubość ściany lewej komory, wielkość lewego przedsionka, gradient ciśnienia skurczowego w drodze odpływu lewej komory). Ponadto, w skali PRIMACY uwzględniany jest również wiek oraz wyniki badań genetycznych [10]. W żadnej ze skali nie wzięto pod uwagę wyników badania elektrokardiograficznego czy odkształcenia ściany (*strain*) lewego przedsionka w badaniu echokardiograficznym co wydaje się być interesujące w kontekście dalszych badań klinicznych.

Niescalenie mięśnia lewej komory odpowiada za około 5% kardiomiopatii dziecięcych i jest uznawane za trzeci najczęstszy typ [4]. Najczęściej stosowane echokardiograficzne kryteria diagnostyczne wg. Jenni i wsp. definiują chorobę jako stosunek części niescalonej do scalonej miokardium >2:1 w fazie skurczu z obecnością nadmiernego beleczkowania i lakun wypełniających się krwią [11].

Ze względu na obecność nadmiernego beleczkowania lewej komory u niektórych sportowców czy kobiet ciężarnych, niektórzy autorzy poddają dyskusji czy niescalenie mięśnia lewej komory jest formą kardiomiopatii czy też cechą osobniczą [1]. Z drugiej strony, z definicji pierwotna nieprawidłowa budowa mięśnia sercowego to właśnie kardiomiopatia. Wytyczne *American Heart Association* uwzględniają niescalenie mięśnia lewej komory jako podtyp kardiomiopatii [12]. Szczególnie interesujący wydaje się być podział niescalenia na podgrupy fenotypowe: łagodne, ze współistniejącą arytmią, ze współistniejącym innym typem

kardiomiopatii, prawokomorowe lub obukomorowe niescalenie, oraz współistniejące z wrodzoną wadą serca [13]. Ze względu na częstość występowania tej cechy u pacjentów pediatrycznych oraz obecność zarówno nagłych zgonów sercowych jak i postępującej niewydolności serca w tej grupie, w niemniejszym opracowaniu zdecydowano się uporządkować i pogłębić wiedzę dotyczącą tego fenotypu [4,14,15].

Kardiomiopatie ze względu na trudny do przewidzenia przebieg choroby są wyzwaniem dla klinicystów. Dostępne dane dotyczące szacowania ryzyka niekorzystnego przebiegu choroby w populacji dziecięcej są ograniczone. Zarówno zapis elektrokardiograficzny jak i badanie echokardiograficzne to łatwo dostępne i mało czasochłonne badania wykonywane podczas rutynowych wizyt kontrolnych u dzieci z kardiomiopatią. Poszukiwanie czynników ryzyka związanych z groźnymi zaburzeniami rytmu czy nasilaniem się niewydolności serca możliwych do zmierzenia podczas najczęściej wykonywanych badań, jest niezwykle istotne w kontekście wyodrębniania chorych wymagających największej uwagi klinicznej. Ponadto, wyodrębnienie czynników elektrokardiograficznych i echokardiograficznych pomagających w odróżnieniu pacjentów z łagodnym fenotypem kardiomiopatii od zdrowych dzieci jest istotne w aspekcie podejmowania decyzji klinicznych dotyczących konieczności dalszej opieki kardiologicznej.

W badaniu poszukiwano nowych czynników ryzyka niekorzystnego przebiegu choroby poprzez przeprowadzenie prospektywnego badania obserwacyjnego. W momencie włączenia do badania u dzieci z kardiomiopatią przerostową, rozstrzeniową oraz niescaleniem mięśnia lewej komory wykonano: 12-odprowadzeniowe badanie elektrokardiograficzne (EKG), 24-godzinne monitorowanie Holter EKG, badanie echokardiograficzne oraz oznaczono stężenie biomarkerów sercowych w surowicy krwi (troponiny I oraz NT-proBNP). Z badania wykluczono pacjentów z kardiomiopatiami wtórnymi do chorób metabolicznych, nerwowo-mięśniowych, syndromicznych (RASopatie), z cechami dysmorfii czy innymi wrodzonymi wadami serca. Pacjentów obserwowano pod kątem niekorzystnego przebiegu choroby definiowanego jako: wystąpienie częstoskurczu komorowego (VT), kwalifikacja do przeszczepu serca czy implantacji urządzenia wspomagającego lewą komorę serca (*left ventricle assist device* - LVAD), kwalifikacja do wszczepienia kardiowertera defibrylatora (*implatable cardioverter defibrillator* - ICD), adekwatne wyładowanie ICD i zgon sercowy. Wyniki badań EKG oraz echokardiograficznych dzieci z kardiomiopatią porównano z wynikami zdrowych dzieci z grupy kontrolnej dobranych pod kątem wieku oraz płci.

W prezentowanych pracach zmienne ciągłe z rozkładem normalnym przedstawiane są jako średnie z odchyleniem standardowym (±SD), pozostałe zmienne ciągłe jako mediany z przedziałem międzykwartylowym (IQR). Zmienne porządkowe i nominalne prezentowane są

jako częstość występowania i wartość procentowa (%). Do analizy różnic pomiędzy zmiennymi ciągłymi stosowane były następujące narzędzia: T-test, test Manna-Whitneya, F-Test i test Kurskala-Wallisa w zależności od liczby i rozkładu zmiennych. Zmienne porządkowe i nominalne zostały porównywane przy pomocy testu chi-kwadrat. Model klasyfikacji lasu losowego zastosowano do zidentyfikowania parametrów pomagających najlepiej przewidzieć punkt końcowy. Krzywe Kaplana-Meiera przedstawiają wszystkich pacjentów z kardiomiopatią, ze względu na niewielką grupę badaną nie wykonywano analizy w podgrupach. Istotność statystyczna zdefiniowana była jako wartość $p<0,05$.

Publikacja I jest przeglądem systematycznym dotyczącym niekorzystnego przebiegu choroby u pacjentów pediatrycznych z niescaleniem mięśnia lewej komory. W artykule podsumowano opisane w literaturze czynniki ryzyka w badaniach: elektrokardiograficznym, echokardiograficznym, rezonansie magnetycznym serca oraz w badaniach genetycznych. Podjęto próbę usystematyzowania dotychczasowej wiedzy oraz wyodrębnienia podgrup pacjentów pediatrycznych wymagających największej uwagi klinicznej. Przedyskutowano różnice w czynnikach ryzyka pomiędzy pacjentami pediatrycznymi, a dorosłymi z LVNC.

Publikacja II przedstawia wyniki analizy zapisów EKG u pacjentów z kardiomiopatią oraz u dzieci z grupy kontrolnej. Omówiono w niej czynniki elektrokardiograficzne związane z niekorzystnym przebiegiem choroby. Szczególną uwagę poświęcono parametrowi kąt QRS-T, który jest parametrem wektrokardiograficznym odzwierciedlającym nieprawidłowości w repolaryzacji i depolaryzacji mięśnia sercowego [16]. Parametr ten powiązano z ryzykiem arytmii komorowej, nasilenia niewydolności serca czy zgonem u dorosłych z różnymi typami kardiomiopatii [17-20]. W populacji dziecięcej badania dotyczące kąta QRS-T w zapisie EKG u pacjentów z kardiomiopatią są nieliczne i dotyczą jedynie dzieci z HCM i LVNC [20-22]. W badaniach tych nie podejmowano próby powiązania wartości kąta QRS-T z przeżywalnością czy oceną przydatności tego parametru w wyróżnianiu pacjentów we wczesnym stadium choroby. Ponadto w publikacji II oceniono wartość biomarkerów sercowych takich jak: NT-proBNP oraz troponina I w szacowaniu ryzyka niekorzystnego przebiegu choroby u pacjentów pediatrycznych z DCM, HCM i LVNC.

Publikacja III stanowi analizę parametrów echokardiograficznych związanych z niekorzystnym przebiegiem choroby u dzieci z kardiomiopatią. W populacji dziecięcej tradycyjne parametry służące do oceny funkcji rozkurczowej lewej komory są niedoskonałe ze względu na zmienność wartości normalnych z wiekiem, trudności w rozróżnianiu zdrowych pacjentów od tych we wczesnym stadium kardiomiopatii oraz słabej zgodności pomiarów między badaczami [23]. W przeprowadzonym badaniu oprócz analizy tradycyjnie mierzonych parametrów funkcji skurczowej i rozkurczowej lewej komory, szczególną uwagę poświęcono

odkształceniu lewego przedsionka w kontekście związku z występowaniem niepożądanych zdarzeń arytmicznych, nasileniem niewydolności serca oraz zgonem. Podjęto próbę porównania parametrów stosowanych do oceny funkcji rozkurczowej z parametrami odkształcenia lewego przedsionka. Doniesienia dotyczące oceny odkształcenia lewego przedsionka metodą śledzenia markerów akustycznych (*speckle tracking echocardiography* - STE) w badaniu echokardiograficznym u dzieci z kardiomiopatią są nieliczne [24,25]. Dotychczas nie opublikowano prac dotyczących związku tego parametru z niekorzystnym przebiegiem choroby u dzieci, dlatego zdecydowano się przeanalizować te parametry we własnym badaniu.

5. ZAŁOŻENIA I CEL PRACY

Głównym celem pracy było poszukiwanie czynników predykcyjnych zaawansowania klinicznego choroby i ryzyka nagłych zdarzeń sercowych u dzieci z trzema najczęstszymi typami kardiomiopatii. Szczegółowe cele badawcze obejmowały:

- Analizę opublikowanych badań dotyczących przebiegu choroby u dzieci z fenotypem niescalenia mięśnia lewej komory (LVNC) i wyodrębnienie czynników powiązanych z jej niekorzystnym przebiegiem **(Publikacja I)**
- Analizę kąta QRS-T w 12-odprowadzeniowym zapisie elektrokardiograficznym u dzieci z kardiomiopatią rozstrzeniową, przerostową i niescaleniem mięśnia lewej komory w celu poszukiwania parametru pomocnego w przewidywaniu niekorzystnego przebiegu DCM, HCM i LVNC **(Publikacja II)**.
- Ocenę odkształcenia (*strain*) lewego przedsionka w badaniu echokardiograficznych u dzieci z HCM, DCM i LVNC w celu poszukiwania parametrów związanych z niekorzystnym przebiegiem choroby oraz ocenę jego przydatności w odróżnianiu dzieci z łagodnym fenotypem od zdrowych dzieci **(Publikacja III)**.
- Analizę stężenia biomarkerów sercowych (troponina I i NT-proBNP) w surowicy krwi u pacjentów z DCM, HCM i LVNC w celu poszukiwania różnic pomiędzy dziećmi z niekorzystnym przebiegiem choroby a tymi z łagodnym fenotypem **(Publikacja II)**.

6. KOPIE OPUBLIKOWANYCH PRAC

PUBLIKACJA I

Left Ventricular Noncompaction-A Systematic Review of Risk Factors in the Pediatric Population

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MDPI

Review

Left Ventricular Noncompaction—A Systematic Review of Risk Factors in the Pediatric Population

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Abstract: Left ventricular noncompaction (LVNC) is a heterogeneous, often hereditary group of diseases, which may have diverse clinical manifestations. This article reviews the risk factors for unfavorable outcomes of LVNC in children, as well as discuss the diagnostic methods and the differences between pediatric and adult LVNC. Through a systematic review of the literature, a total of 1983 articles were outlined; 23 of them met the inclusion criteria. In echocardiography the following have been associated with adverse outcomes in children: Left ventricular ejection fraction, end-diastolic dimension, left ventricular posterior wall compaction, and decreased strains. T-wave abnormalities and increased spatial peak QRS-T angle in ECG, as well as arrhythmia, were observed in children at greater risk. Cardiac magnetic resonance is a valuable tool to identify those with systolic dysfunction and late gadolinium enhancement. Genetic testing appears to help identify children at risk, because mutations in particular genes have been associated with worse outcomes. ECG and imaging tests, such as echocardiography and magnetic resonance, help outline risk factors for unfavorable outcomes of LVNC in children and in identifying outpatients who require more attention. Refining the current diagnostic criteria is crucial to avoid inadequate restrain from physical activity.

Keywords: left ventricular noncompaction; hypertrabeculation; noncompaction cardiomyopathy; children; adolescents

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1. Introduction

Left ventricular noncompaction (LVNC) is a heterogeneous group of diseases morphologically characterized by excessive trabeculations with concomitant deep recesses predominantly present in the left ventricle of the heart [1]. The significance of this finding in imaging studies has been widely debated mostly due to the polymorphic course of the disease, ranging from asymptomatic patients to children who die or undergo cardiac transplant during the first five years after diagnosis, which has been reported in around 6% of cases [2]. Furthermore, the placement of LVNC among cardiomyopathies is inconsistent; on the one hand, the American Heart Association (AHA) lists LVNC as a type of genetic cardiomyopathy together with hypertrophic and arrhythmogenic right ventricular cardiomyopathy [3]. On the other hand, the European Society of Cardiology (ESC) labels LVNC as an unclassified type of cardiomyopathy [4].

Some argue that the current definition of LVNC requires revision, because it is limited only to morphology and does not consider the function of the ventricle or the kind of genetic mutations; thus, suggestions regarding the division of LVNC into subtypes have been made [1,2,5,6]. Towbin et al. [1,5] outlined a classification of LVNC into the following: (1) Isolated LVNC (with normal cardiac function); (2) LVNC with congenital heart diseases (CHD); (3) HCM (hypertrophic cardiomyopathy) with LVNC; (4) DCM (dilated cardiomyopathy) with LVNC; (5) RCM (restrictive cardiomyopathy) with LVNC; (6) HCM-DCM

with LVNC; (7) right ventricular noncompaction; (8) biventricular LVNC; and (9) LVNC with arrhythmia.

In children, the incidence of LVNC is estimated to be 0.11 per 100,000, with the highest incidence below one year of age, and children with isolated LVNC and normal ejection fraction are usually diagnosed at an older age [2,7]. With the improving imaging techniques and greater availability of echocardiography and cardiac magnetic resonance (CMR) the diagnosis is more frequent, and thus, the incidence will increase, with the ensuing risk of overdiagnosis and overtreatment [8]. For this reason, there is an urgent need to outline risk factors, which could help to successfully determine patients who require regular controls, and to concurrently delineate patients who can safely undertake physical activity.

This review presents current knowledge concerning the risk factors for an unfavorable outcome of LVNC in the pediatric population, and discusses the diagnostic methods and differences between pediatric and adult LVNC. To our knowledge, no systematic reviews concerning pediatric LVNC and the variety of its risk factors have been published to date.

2. Material and Methods

A computer search was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) scheme by two independent observers in three major databases (Pubmed, Embase, Cochrane) using the following search terms: (left ventricular noncompaction OR noncompaction OR hypertrabeculation OR LVNC OR NCLV) AND (children OR pediatric OR paediatric or neonate* OR infant* or adolescent*) AND (event* OR MACE OR major adverse cardiovascular event OR heart failure OR heart transplantation OR ICD OR ventricular arrhythmia OR ventricular tachycardia OR ventricular fibrillation OR survival OR outcome OR death OR mortality OR thromboembolism OR stroke) (Figure 1). Articles in which authors outlined risk factors for unfavorable outcomes in pediatric LVNC, such as the following: Progression of heart failure, malignant ventricular arrhythmia (sustained ventricular tachycardia (VT), ventricular fibrillation (VF), or appropriate ICD (implantable cardioverter defibrillator) shock), stroke, cardiac arrest, sudden death, implantation of LV assistance device, ICD implantation or heart transplant were used in our analysis. In our review, we included studies on children and adolescents (from birth to 21 years old). Publications in which either comparison between outcomes in two groups, Kaplan-Meier survival curves, univariate, or multivariate regression analysis was performed were taken into consideration.

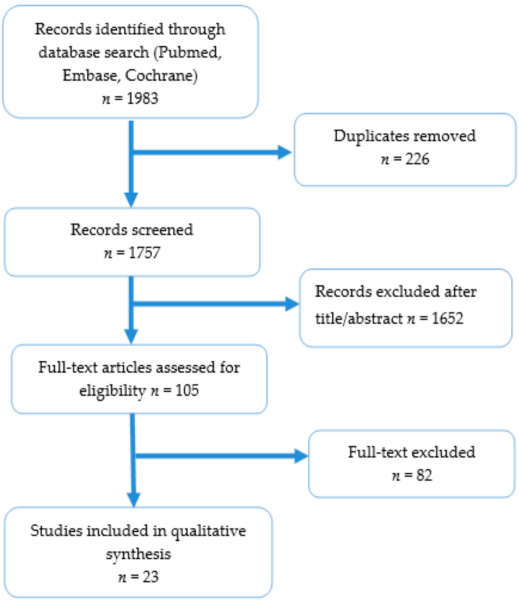

Figure 1. PRISMA search scheme; *n* = number of students.

Case reports, conference abstracts, meta-analyses, systematic reviews, and articles written in languages other than English were excluded from the analysis. To avoid data duplication, publications from the same centers on the same numbers of patients, or on similar numbers of patients with the same conclusions are presented in the summary tables (Tables 1 and 2) only once and were counted only once. One study was excluded, due to the inconsistency in the numerical data. Reports on both adult and pediatric populations, in which data were summed and where it was impossible to differentiate risk factors between the two groups, were not taken into consideration. Articles concerning genetic risk factors were not included in the analysis, due to the recently published meta-analysis by van Waning et al. [9]. The selected studies were independently analyzed by two researchers. The potential risk factors for unfavorable outcomes of LVNC (such as: Cardiac death, implantation of LV assistance device, heart transplant, sustained ventricular tachycardia, ICD implantation, or appropriate ICD shock) were divided into five major categories: Findings related to ECG (electrocardiography), echocardiography, CMR, coexisting heart diseases and other findings. Due to various inclusion criteria, data presentation, and statistical approaches in the outlined articles, no statistical meta-analysis was performed.

3. Results

Altogether 23 out of 1983 articles were considered (Figure 1); no additional records were found through other searches. There were 226 duplicates identified, 1652 records were excluded based on their titles or abstracts, and 82 were eliminated after a full-text revision. The articles included in this review were published between 2004 and 2020 and involved 1812 children with LVNC. The risk factors outlined in the publications are listed in Tables 1–3. Altogether 214 children died (11.8%), and 104 (6%) underwent a heart transplant, and the mean observation time in the outlined publications was 33 months, ranging from 0 to 322 months.

3.1. Echocardiography

Four different echocardiographic diagnostic criteria for LVNC have been used in the studies included in this review (Tables 1 and 2). In four studies, it was not specified, which criteria were used. Moreover, in four studies, more than one diagnostic approach has been used.

In 14 studies of 1081 children, authors analyzed systolic dysfunction of the left ventricle as a risk factor; in 12 of the lower left ventricular ejection fraction (LVEF) or shortening fraction (FS) was associated with a worse outcome (Tables 1 and 2). The lower systolic function of the left ventricle was a risk factor in both children with LVNC without congenital heart diseases (Shi et al. [7], Wang et al. [10], Brescia et al. [11]), as well as in studies including patients with other heart defects (Hirono et al. [12], Hirono et al. [13], Rodriguez-Fanjul et al. [14], Arunamata et al. [15], van Waning et al. [16], Zuckerman et al. [17], Ozgur et al. [18], Punn et al. [19], McMahon et al. [20]). In studies by Gan et al. [21], and Tsai et al. [22], however, LVEF did not prove to be a risk factor. It is of note, that various authors used different cut-off values for significance of left ventricle dysfunction ranging from LVEF < 24% to LVEF < 55%, as well as EF or FS, analyzed as continuous variables in some studies. In the study by Wang et al. [10], performed on over 200 pediatric patients with LVNC (without congenital heart diseases), reduced LVEF was correlated with decreased thickness of the compacted layer in the left ventricular posterior wall, and it was a predictor of death, transplantation, or ICD implantation.

Greater left ventricular end-diastolic dimension (LVEDD) was reported as an unfavorable risk factor in children in five studies of 263 children (Hirono et al. [13], Shi et al. [7], Arunamata et al. [15], Zuckerman et al. [17], and Wald et al. [23]), with various data presentation by different authors (i.e., cut off-values ranging from z-score > 2 to z-score > 8.56; comparison between adverse and benign groups, or hazard ratios with confidence intervals) (Tables 1 and 2). In the study by MacMahon et al. [20], reduced early diastolic tissue Doppler velocity (e') at the lateral mitral annulus was found to be an independent predictor of death or heart transplant. Rodriquez-Fanjul et al. [14], in their report on 14 neonates, 13 of whom had coexisting CHD, mentioned biventricular involvement to be a risk factor for death.

The role of the noncompaction-to-compaction (NC/C) ratio in echocardiography was addressed in seven studies, with a variety of different conclusions, cut-off values for statistical significance, as well as mean NC/C ratios given [7,10,13,17,19,21,23]. In the study by Hirono et al. [13] on 53 children with LVNC and concomitant congenital heart diseases an NC/C ratio >8.33 was a risk factor for death; correspondingly, Wald et al. [23] also suggested adverse outcomes (such as: death, heart transplant, or transplant listing) in patients with NC/C >3. In the study by Gan et al. [21] on 47 patients with isolated LVNC, worse survival was observed in patients with NC/C > 2. Punn et al. [19], in their study including children with CHD, described more segments involved in patients who underwent heart transplant or died; however, no relationship was found with the NC/C ratio. In the study by Shi et al. [7] on children without CHD, the NC/C ratio was borderline significant in terms of outcome ($p = 0.07$). No correlation between outcome and NC/C ratio was found in studies by Wang et al. [10] (who analyzed mean NC/C ratio) and Zuckerman et al. [17] (NC/C $\geq$ 2:1).

In a recent publication by Arunamata et al. [15], which included children with CHD, the significance of speckle tracking echocardiography was raised because radial, circumferential and longitudinal strain were significantly lower in children with LVNC and adverse outcomes, such as: heart transplant or death.

Table 1. Characteristics of patients without congenital heart diseases, as well as echocardiographic, CMR, and other risk factors for unfavorable outcomes.

		Diagnostic Criteria	N	Age Median in Years (IQR)	Deaths/ HTx	Arrhythmia n	Echocardiographic Findings and Risk Factors	CMR Findings and Risk Factors	Other Risk Factors
1	Howard et al., 2019 [24]	Jenni [25]	348	6.8 (0.5–13.8)	31/ 20	SVT—27 (17 in patients with WPW)	lower LVEF in patients with LVNC and WPW than without WPW	-	- No difference in terms of survival between patients with and without WPW - WPW risk factor for cardiac dysfunction
2	Cortez et al., 2019 [26]	Petersen [27]	39	1 (0.8–3) with VA 0.5 (0.2–12) without VA	-	VA—8	-	- LVEDVi greater in patients with VA - LGE was not a predictor of VA	-
3	Shi et al., 2018 [7] /Bharucha et al., 2015 [28]	Jenni [25]	29	age at diagnosis 0.3 (0.1–1.3)	14 /6	-	*** lower FS z-score** *** larger LVEDD z-score** greater LV NC/C in diastole ($p = 0.07$)	-	*** LVNC-D worse prognosis than DCM** *** sporadic LVNC (nonfamilial)** *** female sex**
4	Wang et al., 2017 [10]	Ichida [12]	205	2.7 mo infantile group 7.3 y in juvenile group	23 /9	total—20 VT—11 SSS—5 AF/AFl—4 SVT—5	**** lower LVPWC z-score (≤ −1.5)*** *** LVEF<50% in juvenile**	-	**** CHF at diagnosis*** *** age at onset**
5	Cheng et al., 2015 [29]	Petersen [27]	40	mean 13.7 ± 3	6/ 2	VT/VF—7	-	*** LGE+**	-
6	Brescia et al., 2013 [11]/ Jefferies et al., 2015 [2]	Jenni [25]	242	9 (3 mo–13.8)	31 /13	*** arrhythmia** total—81 VT/VF—42 atrial tachycardia—14 SVT—19 Afl—4	*** LVEF < 55%**	-	*** age at presentation < 1 y** *** LVNC/HCM/DCM phenotype worse prognosis than LVNC with preserved EF, or LVNC/HCM**

* Risk factors for unfavorable outcomes of LVNC have been bolded and highlighted with *. *Justified*—risk factors in multivariable analysis. N—number of patients; mo—months; CHF—congestive heart failure; LVEF—left ventricular ejection fraction; LVEDD—left ventricular end-diastolic dimension; FS—fractional shortening; LVPWC—left ventricular posterior wall compaction; NC/C—noncompaction/compaction ratio; LGE—late gadolinium enhancement; LVEDVi—indexed left ventricular end-diastolic volume; VT—ventricular tachycardia; VF—ventricular fibrillation; SVT—supraventricular tachycardia, Afl—atrial flutter; AF—atrial fibrillation; VA—ventricular arrhythmia; SSS—sinus sick syndrome; WPW—Wolf Parkinson White syndrome; HTx—heart transplant; DCM—dilated cardiomyopathy; HCM—hypertrophic cardiomyopathy.

Table 2. Characteristics of patients with congenital heart diseases, as well as echocardiographic, CMR, and other risk factors for unfavorable outcomes.

		Diagnostic Criteria	N	Age Median in Years (IQR)	Deaths/ HTx	Coexisting CHD n	Arrhythmia n	Echocardiographic Findings and Risk Factors	CMR Findings and Risk Factors	Other Risk Factors
1	Hirono et al., 2020 [13]	Ichida [12]	53	0.3 mo (range 0–14y)	4 /0	53	Total—13 VT—5 SVT—2 AFL—2	* **LVEF < 24%** * **LVEDD z-score > 8.56** * **NC/C at apex > 8.33**	-	* heart failure -children with LVNC and VSD lower EF and more often CHF than children with VSD alone * ***treatment with B-blockers*** * younger age at diagnosis (<84 m) * symptomatic after treatment
2	Hirono et al., 2020 [12]	Ichida [12]	105	7.3 (range 0–16.4)	4 /1	Other cardiac defects—6	PVC—22 VT—1 other—13	* **EF < 55%**	-	
3	Rodriguez-Fanjul et al., 2020 [14]	Jenni [25] and Chin [30]	14	Neonates	6 (5 with CHD) /0	13	VF—1 WPW—1	* **severely depressed systolic function or biventricular involvement**	-	-
4	Gan et al., 2020 [21]	Stollberger [31]	124 (47 with i-LVNC)	NC/C < 2 7.2 (2.2–34 mo) NC/C > 26.8 (3.5–44.5 mo)	15 /0	77	-	* **NC/C > 2 worse survival in i-LVNC** no association between survival and baseline EF	-	-
5	Arunamata et al., 2019 [15]	Jenni [25], Stollberger [31] and Chin [30]	101	2.8 (range 0–19.4)	14 /16	44	-	* **lower LVEF, FS** * **greater LVEDD and LV mass z-score** * **decreased global radial, circumferential and longitudinal strain**	-	* younger age at diagnosis
6	van Waning et al., 2018 [16]	Jenni [25] and Petersen [27]	327 (52 children)	7 (0–14)	8 /4	14	AF—5 sVT/VF—3	* **LV systolic dysfunction** (no differentiation between echo an CMR results)		* genetic and probable genetic LVNC in children * multiple mutations in MYBPC3 * diagnosis < 1 yr LVNC with CHD longer hospitalization and higher perioperative complications rate
7	Ramachandran et al., 2016 [32]	Jenni [25]	26	0.24 (0.01–0.86)	3 /1	26	perioperative arrhythmias—7 CAVB—4 VT/VF—2 nsVT—3	-	-	
8	Czosnek et al., 2015 [33]	n/s	72	mean 13	1 /0	n/s	PVC—37 FAT—1 conduction system disease—1	-	-	Ventricular ectopy more often in patients with EF < 55%
9	Pignatelli et al., 2014 [34]	n/s	10 with Ebstein+ LVNC	Neonates	3 /0	10	-	higher risk of progressive LV dysfunction in patients with LVNC and EA than EA alone	-	* higher risk of adverse outcomes in patients with LVNC and EA than EA alone
10	Zuckerman et al., 2011 [17]	n/s	58	0.3 (range 1d–21y)	11 /15	13	-	* **lower FS** * **greater LVEDD**	-	* hemodynamic instability (requiring mechanical support/inotropic agents)

Table 2. *Cont.*

		Diagnostic Criteria	N	Age Median in Years (IQR)	Deaths/ HTx	Coexisting CHD n	Arrhythmia n	Echocardiographic Findings and Risk Factors	CMR Findings and Risk Factors	Other Risk Factors
11	Ozgur et al., 2011 [18]	n/s	29	mean 4.8 ± 4.6	6 /n/s	7	total—8 PVC—5 VT—1	* lower LV systolic function at diagnosis (p-value 0.058)	-	-
12	Punn et al., 2010 [19]	Jenni [25]	44	range 1d–16y	7 /9	22	VT—2	*** more segments involved** *** lower LVEF, FS**	-	LVNC with significant CHD
13	Tsai et al., 2009 [22]	Chin [30]	46	0.4 (range birth—18.5)	9 /0	36	SVT—3 VT—2 junctional rhythm-3 ectopic atrial rhythm—2	no association between mortality and EF	-	* lower age at diagnosis
14	McMahon et al., 2007 [20]	Jenni [25] and Stollberger [31]	56	4.8 (range 0.3–18)	8 /4	7	total—13 VT—6 SVT—2 AET—3 AF—1 CAVB—1	**** reduced lateral mitral e' velocity*** *** septal e' velocity** *** lateral mitral E/e'** *** lower LVEF**	-	-
15	Hughes et al., 2007 [35]	angiography	31	(range 1 day–2 years)	3 /2	31	-	-	-	* presence of noncomapction * LVNC and single ventricle—worst outcomes
16	Lilje et al., 2006 [36]	Chin [30]	66	4 (range 0–21)	4 (1 with CHD) /n/s	41	total—4	-	-	no difference in terms of mortality between LVNC patients with and w/o CHD
17	Wald et al., 2004 [23]	Jenni [25]	22	mean 3.9 (range 0–16)	3 /2	n/s	AA—2 VA—5	*** increased LVEDD at presentation** *** NC/C ratio > 3**	-	-

* Risk factors for unfavorable outcomes of LVNC have been bolded and highlighted with *. *Justified*—risk factors in multivariable analysis. n/s-not exactly specified. N—number of patients; mo—months; CHD—congenital heart diseases; CHF—congestive heart failure; LVEF—left ventricular ejection fraction; LVEDD—left ventricular end-diastolic dimension; FS—fractional shortening; NC/C—noncompaction/compaction ratio; VT—ventricular tachycardia; sVT—sustained ventricular tachycardia; nsVT—nonsustained ventricular tachycardia; SVT—supraventricular tachycardia; CAVB-complete atrioventricular block; AFL—atrial flutter; AF—atrial fibrillation; AA—atrial arrhythmia, VA—ventricular arrhythmia; PVC—premature ventricular contraction; AET—atrial ectopic tachycardia; WPW—Wolf Parkinson White syndrome; FAT—focal atrial tachycardia; i-LVNC—isolated LVNC; HTx—heart transplant; VSD—ventricular septal defect; EA—Ebstein anomaly.

3.2. Cardiac Magnetic Resonance Imaging

Altogether in three studies, the role of CMR was addressed (Tables 1 and 2). In the study by Cheng et al. [29] on adolescents without CHD (mean age 14 years), LGE (late gadolinium enhancement) was a predictor of adverse outcomes (such as death or heart transplant). Cortez et al. [26], in their study on younger children without congenital heart diseases (mean age 1 year) did not outline LGE as a risk factor for sustained ventricular tachycardia, however, they observed greater LVEDVi (indexed left ventricular end-diastolic volume) in patients with this type of arrhythmia. Van Waning et al. [16], in their analysis of both echocardiographic and CMR results, suggested an association between LV systolic dysfunction and worse outcome in children (including those with CHD); the role of LGE was not assessed.

3.3. Electrocardiography and Arrhythmia

Table 3 shows the ECG results that were presented in 12 studies [10–14,16,21–24,26,29]; abnormal ECG findings were present in 56–100% of children with LVNC, with the most common being the following: Abnormal T-wave, the fulfillment of the voltage criteria for ventricular hypertrophy, and ST-abnormalities. In the study by Brescia et al. [11] on 242 children without CHD T-wave inversion and ST-segment abnormalities were noted as a risk factor of death or transplantation. Hirono et al. [12] mentioned T-wave abnormalities in first graders to be associated with worse outcomes, such as: Death or heart transplant. Moreover, in the study by Cortez et al. [26] on children without CHD, higher heart rate and spatial QRS-T angle $\geq 147^{\circ}$ in children with LVNC were said to be risk factors for sustained ventricular arrhythmia.

Howard et al. [24] showed a relationship between Wolf-Parkinson-White (WPW) pattern on ECG and lower LVEF in children with isolated LVNC; the latter improved in some children after catheter ablation. No statistical significance in terms of survival was observed between children with LVNC and WPW and those without WPW.

The occurrence of arrhythmias in children with LVNC varied from 5% to 34%, depending on the abnormalities considered (Tables 1 and 2). According to Brescia et al. [11], its presence (among children with and without CHD) was associated with an increased risk of death. In the study by Czosnek et al. [33], decreased systolic function of the left ventricle was associated with an increased ventricular ectopy.

Table 3. Most common ECG abnormalities and risk factors for unfavorable outcomes.

	N	Abnormal ECG	Abnormal T-Wave	Abnormal ST	Fragm. QRS	J Wave	VH	RBBB	LBBB	WPW/ Preexciation	LQT	Other	Risk Factors
Hirono et al. [13]	53		8	3	16	7		10	3	1	5	pathologic Q wave—7 AVB 3rd—4	
Hirono et al. [12]	146		6	2	49	23		16	4	0		axis deviation—18 pathologic Q wave—1 AVB—1	* **T-wave abnormality in first graders**
Rodriquez-Fanjul et al. [14]	14	9		2			6			1			
Gan et al. [21]	47	27 [1]											
Howard et al. [24]	348									38			
Cortez et al. [26]	38		33/23 [2]									AVB 3rd—1	* **spatial peak QRS-T angle > 147 degrees**
van Waning et al. [16]	52							5	1			AVB 1st—2 brady—3	
Wang et al. [10]	205	115							7	10	3	AVB 3rd—8	
Cheng et al. [29]	40	36											
Brescia et al. [11]	242	210	94	82			100		1	20	22	atrial enlargement—46 left axis deviation—22	* **ST abnormality** * **T-wave inversion**
Tsai et al. [22]	35	28 [1]					19/15 [3]	2		3	4	AVB 1st—4 interventricular conduction delay-3 enlarged chamber dimension—16	
Wald et al. [23]	22	22	3						1	1			

* Risk factors for unfavorable outcomes of LVNC have been bolded and highlighted with *. VH—ventricular hypertrophy; RBBB—right bundle branch block; LBBB—left bundle branch block; WPW—Wolf Parkinson White syndrome; LQT—long QT; AVB atrioventricular block, brady—bradycardia; [1] abnormal ECG and arrhythmia together. [2] division into later and inferior abnormalities of the T-wave. [3] Right VH/Left VH.

3.4. Coexistence with Other Heart Diseases

Children with LVNC and coexisting congenital heart diseases were included in 15 studies; in six of them, it was impossible to define whether deaths and cardiac transplants occurred among children with or without CHD. In six studies, children with heart defects were excluded from the analysis (Table 1), and in two studies, it was not clearly stated whether children with CHD were included. The mortality rate among children with LVNC and CHD in comparison to children with isolated LVNC was similar (14.2% vs. 13.3%); the percentage of children who underwent cardiac transplant was 4.4% vs. 6.7%, respectively. Both studies that were only on children with isolated LVNC, as well as in those including LVNC with congenital heart diseases decreased left ventricular systolic function, as well as enlarged left ventricular end-diastolic dimension, were associated with worse outcomes.

In six studies, the coexistence of various CHDs with LVNC was analyzed, and in most of them, it was associated with adverse outcomes (Tables 1 and 2). In the study by Ramachandran et al. [32], the coincidence of LVNC and CHD was a risk factor for longer hospitalization, as well as a higher perioperative complication rate in the pediatric population. Hirono et al. [13] outlined that children with LVNC and VSD (ventricular septal defect) tended to have lower LVEF and more often presented with congestive heart failure than patients with VSD only. Similarly, in the study by Pignatelli et al. [34], children with LVNC and Ebstein's anomaly tended to have a worse prognosis and lower LVEF than patients with CHD only, while in the study by Hughes et al. [35], patients with LVNC and single ventricles had worst outcomes in terms of mortality. Punn et al. [19] also outlined that death or heart transplant was more common among patients with severe congenital heart diseases. In the study by Lilje et al. [36], in which children with LVNC were observed for 12 months, no statistical significant difference in terms of mortality was observed between children with coexisting CHD and children with isolated LVNC; thus, in both groups, the disease progressed as the number of patients with congestive heart failure increased during the observation period from 41% to 68%.

In three studies, the issue of the coexistence of another phenotype of cardiomyopathy as an unfavorable risk factor was raised (Table 1). According to Brescia et al. [11], children with mixed phenotypes, such as LVNC/HCM/DCM, had worse prognosis in comparison to patients with LVNC with preserved LVEF or LVNC/HCM phenotype. In the study by Shi et al. [7], children with mixed LVNC-DCM phenotype had a 2-fold higher risk of death than patients presenting with only DCM. In a study on 348 patients, Howard et al. [24] also outlined dilated phenotype as a risk factor for cardiac dysfunction in a univariate analysis. The coexistence of another phenotype of cardiomyopathy was outlined as a risk factor for unfavorable outcome only among patients without coexisting congenital heart diseases.

3.5. Other Risk Factors

In the study by Wang et al. [10] on 205 children with LVNC without CHD, it was shown that children with congestive heart failure at diagnosis are at greater risk for death, a heart transplant, or ICD implantation. Hirono et al. [13], in their study on children with LVNC and CHD, concluded that the presence of heart failure, not necessarily at diagnosis, is a risk factor for death in this group. However, in studies by Gan et al. [21], Shi et al. [7], and Hirono et al. [12] (on school children), patients symptomatic at diagnosis were not at greater risk.

Furthermore, younger age at diagnosis, defined by different authors variously (<1 year old, <84 months, or comparison between median age between benign and adverse groups), was associated with unfavorable outcomes in studies by Hirono et al. [12], Arunamata et al. [15], van Waning et al. [16], Wang et al. [10], Brescia et al. [11], and Tsai et al. [22] (studies on both children with and without congenital heart diseases as listed in Tables 1 and 2). However, in reports by Shi et al. [7] on children with isolated LVNC and Punn et al. [19] (including children with CHD) age at diagnosis was not associated with adverse outcomes.

4. Discussion

4.1. The Role of Echocardiography

Echocardiography is a basic tool used in the diagnosis of LVNC. Multiple diagnostic criteria have been outlined, with those according to Jenni et al. [25] (presence of multiple trabeculations, deep intertrabecular recesses, and thickness of the noncompacted to compacted myocardium in systole (NC/C) > 2:1) are the most commonly used in the pediatric and adult populations; thus, it is of note that in the original criteria congenital heart diseases excluded the diagnosis of LVNC [25,37]. Some authors suggest that in children, the criteria according to Chin et al. [30] (ratio between the epicardial surface to trabeculation base and epicardial surface to trabeculation peak in end-diastole [X/Y]) are more reliable [38]. Other diagnostic criteria that were found in the reviewed literature included those according to Stollberger et al. [31] (presence of >3 trabeculations at end-diastole, which moved synchronously with the compacted myocardium and presence of perfusion on color Doppler of the intertrabecular spaces) and Ichida et al. (NC/C > 2 measured at end-diastole, deep intertrabecular recesses with blood flow visualized on color Doppler)—the latter were mentioned in publications by Hirono et al. [12,13]. However, the original article was impossible to trace. Altogether four different diagnostic echocardiographic criteria and their combinations were used in the studies included in this review, which underlines the indisputable need for international, consistent guidelines concerning the diagnosis of LVNC in pediatric patients. Even though the criteria overlap with each other, some require measurement of the intertrabecular recesses in systole, while others in diastole. Moreover, there has been no consensus regarding the echocardiographic projections; some measure the NC/C ratio in the short axis, while others in the apical view, which further underlines the need for international consensus.

Adult patients with LVNC and lower left ventricular ejection fraction (LVEF) are at higher risk of adverse cardiovascular events [39]. Likewise, in the pediatric population cardiac dysfunction is a risk factor for ventricular arrhythmia, death, or transplantation [7,11,13,17,28,33]. In a retrospective study by Brescia et al. [11], out of 242 children diagnosed with LVNC, 62% presented with or developed systolic ventricular dysfunction, which delineates the severity of the problem.

Unlike in the adult group, in which no correlation between the severity of trabeculations and death was found, the data concerning the role of NC/C ratio are inconsistent in the pediatric population and require further research [39]. LVPWC (left ventricular posterior wall compaction) seems to be another interesting echocardiographic parameter that warrants exploration because decreased posterior wall compaction was correlated with an increased cardiovascular risk and decreased ejection fraction of the left ventricle [10]. In one study by Hirono et al. [13] on children with LVNC and ventricular septal defects, a significant decrease of LVPWC was observed over time; however, the significance of this finding is yet to be determined.

Speckle tracking imaging in adults may be beneficial in differentiating patients with LVNC and normal EF from healthy individuals with LVNC-like traits because in a study by Cortes et al. [40], rigid body rotation (RBR) (rotation at the basal and apical level in the same direction instead of typical clockwise rotation at the basal and anti-clockwise at the apical level) was observed in some patients with LVNC with EF>50%, and is correlated with decreased global longitudinal strains (GLS). This sheds new light on possible future research directions, especially considering that children with LVNC and adverse outcomes had significantly lower values of radial, circumferential, and longitudinal strains [15].

Echocardiography, with its wide accessibility, seems to be a valuable tool in delineating children at higher risk. Regardless of decreased LVEF, lower LVPWC, higher LVEDD, and lower myocardial strain as risk factors for adverse outcomes in children, it is worth mentioning that thromboembolic events are indisputably associated with decreased EF. The importance of prophylaxis implementation is of note because this complication may also occur among pediatric patients [10].

4.2. The Role of CMR

The most common CMR criteria used for diagnosis of LVNC both in the adult and pediatric populations are the one by Petersen et al. (NC/C ratio > 2.3 in end-diastole) [27]. The role of CMR has been expanding, especially in light of reports concerning low reproducibility of echocardiography in LVNC diagnosis, as well as the superiority of CMR over echocardiography in detecting LVNC and assessing its spatial morphology and the extent of trabeculations [41–44]. On the other hand, the current criteria are imperfect because they may lead to overdiagnosis. In the study by Weir-McCall et al. [45], up to 20% of 1651 adult participants fulfilled one criterion for LVNC. Conversely, when extended to four diagnostic criteria (long axis compaction at end-diastole $\geq$2.3, short axis compaction in diastole $\geq$3, and in systole $\geq$2, noncompaction myocardial mass >20%) less than <1% were diagnosed with LVNC [45]. This underlines the importance of performing additional exams in patients with borderline criteria.

The data concerning the accuracy of echocardiography and CMR in the pediatric population are limited and inconsistent; in some studies, LVNC was diagnosed more commonly in echocardiography, in others, the superiority of CMR was outlined [46,47]. Undisputedly, one should consider the complementary value of both methods in diagnosing LVNC in the pediatric population, especially when borderline cases are at stake. Possibly innovative developing techniques in echocardiography, such as 3-dimensional echocardiography and speckle-tracking, combined with CMR, may be of use in determining the diagnosis and differentiating normal variants from pathological changes.

The segmental involvement in the pediatric population is similar to the one observed in adults; unsurprisingly, wider involvement is associated with lower ejection fraction [48]. In the adult population, patients with late gadolinium enhancement (LGE) presented with worse outcomes than those without [49]. In a meta-analysis by Grigoratos et al. [49], no unfavorable outcomes were observed in adult patients with LVNC, normal LVEF, and negative LGE. In contrast to the adult population, the role of LGE as a predictor of arrhythmia risk in the pediatric population is questionable. The different results obtained by Cortez et al. [26] and Cheng et al. [29] may be explained by the different ages of patients analyzed, with adolescents presenting more frequently with LGE. This seems to be in agreement with reports that LGE does not occur in neonates and young children with LVNC; thus, LGE may be a valuable tool in risk stratification in older patients, whereas the search for other traits in the younger population needs to be continued [50].

4.3. ECG

Electrocardiogram (ECG) is an easily accessible tool that is valuable not only in the diagnosis, as was indicated in a Japanese study where 42% of pediatric patients with LVNC were diagnosed, due to school ECG screening, but also in outlining higher risk patients with LVNC [11,12]. Some differences in ECG between adult and pediatric populations can be outlined; the most common ECG abnormalities in the adult population despite ventricle hypertrophies and depolarization abnormalities were bundle branch blocks and AV blocks, which were not as common in the pediatric population [37]. In adults, QTc prolongation in ECG has been observed in up to 44% of patients and has been associated with lower LVEF, increased fibrosis, as well as unfavorable prognosis [51]. The frequency of prolonged QTc interval in ECG in children varies between 9–40% (in our review 9–11%); however, its meaning has not been determined [10,11,22,52]. The differences in ECG abnormalities in the two populations suggest that adult data cannot be routinely applied to the pediatric population; furthermore, ECG aberrations possibly change with age and progression of LVNC or may be associated with the distinct underlying pathophysiology of the disease, because genetic mutations are more common in children than in adults [16].

It is of note that the occurrence of malignant arrhythmia (such as sustained ventricular tachycardia (sVT) or ventricular fibrillation (VF)) may be an independent risk factor for unfavorable outcomes, because adult patients with LVNC after ICD implantation as a secondary prophylaxis commonly presented with normal ejection fraction [53]. A similar

trend was observed in children. In the study by Brescia et al. [11], not all patients who experienced sudden cardiac death had ventricular dysfunction. These findings point toward a subgroup of patients with LVNC, who have preserved cardiac function and concomitant malignant arrhythmias, and for this reason, require special attention. Genetic testing might be of use in outlining higher risk patients, because mutations in genes that are typically associated with channelopathies, such as long QT-interval or catecholaminergic VT, have been detected in patients with LVNC; interestingly, in some patients, features of LVNC were not present at diagnosis and developed with time [6].

4.4. Coexistence with Other Heart Diseases

Because LVNC is heterogeneous in its image, it may coexist with other types of cardiomyopathy or progress to a mixed form, which was observed in 12% of cases within two years in the study by Jefferies et al. [2] on the cardiomyopathy registry in the USA and Canada. Some authors suggest that the nomenclature should include prior cardiomyopathy with coexisting LVNC traits because the latter describes only morphological features; this could simplify the classification and help to delineate higher risk patients [54]. Nevertheless, children with LVNC concomitant with other phenotypes of cardiomyopathy frequently present with heart failure and have a worse prognosis, among whom children with coexisting DCM or indeterminate cardiomyopathy present with the worst outcomes [2]. This seems to be in agreement with the observations made by some authors that greater LVEDD was associated with worse outcomes in children [7,13,15,17,23]. The burden of the need for clear classification of LVNC prevails, as some authors outlined mixed forms of LVNC, such as LVNC-DCM type, while others pointed out only echocardiographic traits characteristic for DCM, i.e., increased LVEDD. It is of note that, in contrast to the pediatric population, worse outcome of patients with mixed phenotype has not been confirmed unequivocally in adult studies, which once again points toward possible differences in adult and pediatric LVNC [9,55].

Furthermore, LVNC can coexist with different congenital heart diseases (CHD), varying from mild types, such as patent ductus arteriosus or septal defects to more severe, i.e., Ebstein's anomaly or hypoplastic left heart syndrome (HLHS) [5]. Familial occurrence has been reported with some family members presenting with pure LVNC, while others with concomitant CHD [6]. Patients with CHD and LVNC tend to have a worse prognosis, require longer hospitalizations, and more frequently present with postoperative complications than children with CHD only, which points toward a sub-group of patients requiring more attention [13,32]. However, a large meta-analysis concerning the survival of children with isolated LVNC, as well as those with coexisting CHD, is necessary to draw clear conclusions, as comparing mortality and transplantation rates from 16 studies showed no significant differences between the two groups. It is of note that LVNC has been reported to occur more frequently among children with heterotaxy syndrome, with a prevalence of 7.5% vs. 0.013–1.3% in the general population, which may suggest a common genetic mechanism [56].

4.5. Other Risk Factors

Influence of Medical Treatment

Reports concerning the effect of medical treatment on ECG and echocardiography are inconsistent. In a small study on 20 adults, 13-month treatment with β-blockers did not significantly influence the ECG or the LVEF; however, it led to a reduction in the LV mass [57]. In scarce pediatric reports, medical therapy with angiotensin-converting enzyme inhibitors (ACE-I), angiotensin II receptor blockers, β-blockers, or combinations of the former has been associated with an improvement of the ejection fraction and a decrease in the size of the left ventricular diastolic dimension, which points towards a favorable remodeling effect [58,59]. Treatment with carvedilol has been shown to improve left ventricular function; however, the long-term influence of medication on the survival of children with LVNC has not been assessed [23].

Due to familial occurrence of LVNC in around 30% and familiar history of SCD in 18% of children with LVNC, genetic testing, and detailed familiar background may help determine higher risk patients with accidentally found LVNC [2,10,60]. A positive genetic profile is more common in children than in adults, with the latter more likely to have sporadic LVNC, whereas in children, abnormalities in chromosomes, and x-linked and mitochondrial genes are more prevalent [9,16]. Moreover, in contrast to adults, genetically confirmed pediatric LVNC has been associated with worse outcomes [16].

Among family members of patients with different cardiomyopathies hypertrabeculation of the myocardium is the most common abnormality, which suggests that noncompaction is a morphological finding that can develop into cardiomyopathy in the future, and that the formation of LVNC is a continuous process [61]. Conversely, due to the presence of healthy subjects with trabeculations in the LV, genetic profiling may assist in identifying pathogenic mutations and in differentiating subjects at risk. Knowledge of the genetic background may be of importance in determining the progression of the disease because certain mutations in genes, i.e., DMD (Duchene muscular dystrophy), are associated with the dynamic course of the disease and progression in the trabeculations and severity of heart failure time [6]. Waning et al. [9], in their systematic review on adults and children, outlined that the presence of mutations in some genes (such as MYBPC3, TTN, arrhythmia, and nonsarcomere nonarrythmia genes and X-linked genes) was associated with an increased risk of adverse events, whereas patients with most common mutations in MYH7 were at a lower risk. Furthermore, genetic testing may help outline patients at greater risk of severe heart failure because the presence of genetic mutations in genes associated with cardiomyopathies has been linked to lower ejection fraction [16,62]. In a study on adults and children, a greater number of genetic variants of interest (VOI) was associated with lower LVEF and greater NC/C ratio in MRI [63].

Unequivocally, the current criteria for the diagnosis of LVNC require revision. Perhaps it would be reasonable to include abnormal ventricle function, the presence of arrhythmia, as well as genetic information into the scheme in the future. Conversely, one must keep in mind the risk of overdiagnosis, especially in the adult population [45]. The AHA/ACC recommendations for competitive athletes with cardiovascular diseases do not restrain asymptomatic patients with LVNC with normal left ventricular systolic function, without significant ventricular arrhythmias, and without unexplained syncope from participation in competitive sports [64]. Similar conclusions have been drawn in the pediatric population, because patients with such characteristics are perceived to have a low risk of sudden cardiac death, and for this reason, they are not restricted from sporting activities [11].

4.6. Study Limitations

The limitations of the study include selection bias and possible duplication of data because some reports were from the same centers, but from different years. Furthermore, due to the lack of international consensus, we included studies that used different diagnostic criteria for LVNC, which may result in an increased diversity of the groups presented. Another limitation is the lack of statistical metanalysis; heterogeneous data, as well as different cut-off values and approaches to data presentation (i.e., different echocardiographic parameters measured, with LVEF presentation ranging from LVEF<55% to LVEF<24%, or some authors calculating LVEF as a continuous variable) restricted the statistical analysis.

5. Conclusions

ECG and imaging tests, such as echocardiography and magnetic resonance, help outline risk factors for unfavorable outcomes of LVNC in children, as well as dividing patients into subgroups at risk, such as the following: Those with known genetic mutations, coexisting cardiomyopathies, congenital heart diseases, decreased EF, greater LVEDD, as well as patients with ECG abnormalities and arrhythmia. It is noteworthy that some differences between adult and pediatric LVNC in terms of ECG, echocardiographic, CMR, and genetic test results can be outlined, with the latter presenting with worse outcomes

when mixed cardiomyopathy traits or genetic mutations are present. Increased genetic testing will help to improve the knowledge concerning genetic variants and assist in identifying more patients at risk.

Undoubtedly, the burden of pediatric LVNC prevails, and an international consensus is essential, because the current diagnostic criteria are inconsistent and do not unequivocally point outpatients who do not require special attention from health care professionals and can safely undertake physical activity.

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Electrocardiographic Parameters Associated with Adverse Outcomes in Children with Cardiomyopathies

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Electrocardiographic Parameters Associated with Adverse Outcomes in Children with Cardiomyopathies

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Abstract: Cardiomyopathies have a low prevalence in children and thus may lead to malignant ventricular arrhythmias or the progression of heart failure, resulting in death. In adults, the QRS-T angle derived from ECG has been associated with adverse outcomes in patients with hypertrophic and dilated cardiomyopathies. We aimed to assess the electrocardiographic parameters, including QRS-T angle, associated with adverse cardiac events in children with cardiomyopathies. Forty-two children with cardiomyopathies were included in this study: 19 with dilated cardiomyopathy, 17 with hypertrophic cardiomyopathy, and 6 with left ventricular non-compaction. Additionally, 19 control subjects were recruited. In terms of ECG parameters, the QRS-T angle was significantly greater among patients with adverse outcomes compared to patients without the end points of the study (133° vs. 65°, $p < 0.001$). On Kaplan–Meier survival curves, QRS-T angle > 120°, increased serum concentrations of NT-proBNP and troponin I levels as well as greater NYHA or Ross scale were associated with the greatest risk of unfavorable outcome. The QRS-T angle appears to be a valuable component of 12-lead ECG interpretation, and might be helpful in outlining patients with the greatest cardiovascular risk. Additionally, serum biomarkers such as NT-proBNP ($p = 0.003$) and troponin ($p < 0.001$) are useful in outlining patients with the worst survival.

Keywords: hypertrophic cardiomyopathy; dilated cardiomyopathy; left ventricular non-compaction; QRS-T angle; electrocardiography; pediatric; children

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1. Introduction

Vectorcardiography (VCG) is a field of electrocardiography that describes the direction and magnitude of the electrical forces conducted between cardiomyocytes [1]. The QRS-T angle can be calculated between the vector of depolarization (QRS-complex) and repolarization (T wave) providing information about the myocytes' electrical conductivity and action potential's heterogeneity [1]. Abnormal conduction will result in an increased QRS-T angle, even though standard 12-lead ECG (electrocardiogram) may not show any specific abnormalities.

In adults with non-ischemic dilated cardiomyopathies, a greater QRS-T angle is a risk factor for ventricular arrhythmias, re-hospitalizations due to heart failure, and increased mortality [2–4]. A similar observation was made in patients with hypertrophic cardiomyopathy (HCM) in whom a wider QRS-T angle was associated with greater risk for ventricular arrhythmia [5,6]. Furthermore, an association between some genetic mutations (LZTR1, LGMD, SCN5a) and ion channel abnormalities of the myocytes was shown for cells with dilated and hypertrophic cardiomyopathies [7–9]. Electrical instability of the myocardium, possibly due to genetic predisposition leading to ion channel instability,

fibrosis, or abnormal stretching of the myocardial cells, can be assessed with a greater QRS-T angle.

It is of note that ventricular tachycardia in children may also be caused by channelopathies. Models helpful in understanding the pathophysiology and treatment of SQTS are being developed [10]. Furthermore, cell studies shine new light on optimizing pharmacotherapy in SQTS and Brugada Syndrome [11,12]. Considering the growing understating of pathophysiology and treatment of channelopathies, they should be excluded in all children with ventricular tachycardia, especially, that overlapping of cardiomyopathy and channelopathy genes has been reported [13]. In all hypertrophic, dilated and left ventricular non-compaction cardiomyopathies, ventricular arrhythmia may occur and heart failure may progress, resulting in death. The literature on the usefulness of the QRS-T angle in children with hypertrophic and non-compaction cardiomyopathies is limited [14,15]. To our knowledge, the QRS-T angle in children with idiopathic dilated cardiomyopathy (DCM) has not been assessed previously.

In our study, we focused on hypertrophic, dilated and left ventricular non-compaction cardiomyopathies because they are the most common among children [16]. We hypothesized that repolarization and depolarization abnormalities assessed by QRS-T angle may help to predict not only arrhythmia but also abnormal ventricular function, heart transplant qualification, or death. We aimed to assess electrocardiographic factors associated with unfavorable outcomes of pediatric dilated, hypertrophic, and left ventricular non-compaction cardiomyopathies.

2. Materials and Methods

In this single-center prospective study, we included 42 children with cardiomyopathies: 19 with idiopathic dilated cardiomyopathy (DCM), 17 with hypertrophic cardiomyopathy (HCM) and 6 with left ventricular non-compaction (LVNC). Additionally, 19 healthy, gender- and age-matched subjects were recruited.

The diagnosis of cardiomyopathy was stated on the basis of echocardiography; in borderline cases cardiac magnetic resonance imaging (CMR) was used for verification. Dilated cardiomyopathy was defined as enlargement of the left ventricle with a z-score > 2 combined with reduced ejection fraction (<55%). Secondary causes such as: aortic stenosis, coarctation of the aorta, or anomalous coronary arteries were excluded in all patients [16]. Hypertrophic cardiomyopathy was diagnosed according to the ESC 2014 criteria and defined as a wall thickness z-score > 2 [17]. Left ventricular non-compaction cardiomyopathy was identified using criteria from Jenni et al., i.e., non-compaction to compaction ratio > 2 in systole [18].

The control group consisted of healthy children with normal echocardiographic examinations. The exclusion criteria of participating in the study were co-existing congenital heart defects, syndromic cardiomyopathies, co-existing chronic diseases, dysmorphic features, and lack of consent to participate in the study.

According to the study protocol, all patients had a 12-lead electrocardiogram (ECG), 24 h ECG Holter monitoring, and echocardiography performed at the beginning of the study. Additionally, serum concentrations of cardiac biomarkers (highly sensitive troponin I and N-terminal prohormone of brain natriuretic peptide (NT-proBNP)) were measured in children with cardiomyopathies. Symptoms of heart failure were assessed using the NYHA scale or Ross scale in younger children [19]. Data concerning the previous history of ventricular tachycardia were also collected. An unfavorable outcome of the disease was defined as a major adverse cardiac event (MACE) and included the following: cardiac death, qualification for heart transplantation, left-ventricular assist device (LVAD) implantation, or the occurrence of ventricular tachycardia. Furthermore, the end points of the study were divided into heart failure end points (death due to progression of heart failure, qualification for heart transplantation) and arhythmic end points (ventricular tachycardia, sudden cardiac death, qualification for an ICD (implantable cardioverter defibrillator) implantation).

The study was approved by the University Bioethical Committee. It was registered at ClinicalTrial.gov (NCT04316923). All parents or guardians, as well as patients aged 16 years or older, signed a written informed consent form prior to participating in the study.

2.1. Electrocardiography (ECG)

Twelve-channel electrocardiograms were performed using 50 mm/s speed and 10 mm/mV amplitude for limb and precordial leads. The electrocardiograms were analyzed by 2 independent observers, and discrepancies were resolved by a third reviewer. In each electrocardiogram heart rhythm, heart rate, heart axis, atrial and ventricular hypertrophy, duration of: PQ, QRS, QT and QTc intervals, Q wave abnormalities, ST changes, T wave abnormalities, and spatial QRS-T angle were assessed. QTc was calculated using Bazzett's formula.

The spatial QRS-T angle was assessed according to the previously described Kors' quasi-orthogonal transform method using visual estimation of the limb and precordial leads [20,21]. Patients with bundle branch blocks were excluded from the QRS-T analysis [21].

2.2. Echocardiography

Echocardiography was performed using a Philips EPIQ ultrasound system 9.0.1 (Koninklijke Philips N.V., Amsterdam, The Netherlands) with X5-1, S5-2, and S8-3 transducers. The left ventricular ejection fraction (LVEF) was assessed using Simpson's method. The left ventricular internal diastolic diameter (LVIDd) and left ventricular posterior wall thickness in diastole (LVPWd) were evaluated using M-mode; *z*-scores were used to adjust for differences in body weight and height [22].

2.3. Statistical Analysis

Continuous variables with normal distribution are presented as mean and standard deviation (SD); when skewed distribution is present the median and inter quartile range (IQR) are given. Categorical variables are presented as frequencies and percentages. The statistical analysis was performed using R version 4.1.2 (1 November 2021), GNU General Public License. Continuous variables were compared using T-test, Mann–Whitney U test, F test, and Kruskal–Wallis test, depending on the number and distribution of the compared variables. Categorical variables were compared using the Chi-Square test.

Correlations were assessed using Pearson's or Spearman's coefficient, depending on the distribution of variables. A random forest model was used to outline the most useful parameters in predicting adverse outcomes in all cardiomyopathy patients as well as in the HCM and DCM groups. Due to the limited number of patients included in the study Kaplan–Meier survival analysis was calculated including all cardiomyopathy patients. The factors associated with unfavorable outcomes could not be calculated separately for the LVNC group due to a limited number of patients.

Lin's correlation coefficient was used to compare the accuracy of the ECG measurements between 2 observers. A p-value < 0.05 was considered statistically significant.

3. Results

Forty-two children with cardiomyopathies (19 with DCM, 17 with HCM, 6 with LVNC) and 19 healthy control subjects were included in the study. The median age among children with cardiomyopathies was 10 years (IQR 3–15 years), there were 23 females, and the mean time of observation was 13 months. There were no significant differences in terms of gender, age, and BSA between the control subjects and the HCM, DCM and LVNC patients. The groups' characteristics are presented in Table 1.

Table 1. Patients' characteristics.

	DCM $n = 19$	HCM $n = 17$	LVNC $n = 6$	Control $n = 19$	p-Value
gender (n female/male)	10/9	8/9	5/1	10/9	0.49
Age (years)	8 (3–14)	10 (3–16.5)	10.5 (8–15.5)	8 (4–15)	0.73
BSA (m^2)	1.1 (0.6–1.8)	1.5(0.6–1.9)	1.1(0.9–1.3)	1.2(0.7–1.7)	0.85
observation time (months)	14 ± 8	11 ± 7	12 ± 8	n/a	0.42

Data are presented as median and IQR in parenthesis or mean and standard deviation (±), n—number of patients; DCM—dilated cardiomyopathy, HCM—hypertrophic cardiomyopathy, LVNC—left ventricular non-compaction, BSA—body surface area, n/a—not assigned.

Baseline 12-lead ECGs were not significantly different among DCM, HCM, and LVNC patients in terms of heart rate, PQ, QRS, and QTc intervals as well as QRS-T angle (Table S1 Supplementary Materials). None of the patients presented with short QTc interval. Based on genetic testing and clinical investigation no one fulfilled criteria for LQTS.

When compared to the control group, DCM patients did not differ in terms of heart rate, PQ, QRS, and QTc interval; however, they presented with a wider QRS-T angle (75° vs. 41° $p = 0.007$). In the HCM group heart rate, PQ and QRS intervals were not significantly different from the control group. Thus, a greater mean QTc interval (420 vs. 380 ms $p = 0.002$), QRS-T angle (100° vs. 41° $p < 0.001$), and two or more negative T waves ($p = 0.005$) were observed more frequently in HCM patients than in the control group. The LVNC group did not differ from the control group in terms of heart rate, PQ, and QRS duration. Thus, a greater QTc interval (420 vs. 380 ms $p = 0.008$) as well as greater QRS-T angle (64° vs. 41° $p = 0.03$) were observed in patients with LVNC in comparison with the healthy control subjects.

Adverse outcomes were observed in 13 patients; among DCM patients, six qualified for a heart transplant, two of them died while awaiting heart transplant, ventricular arrhythmias were observed in four patients, and two of them received an ICD. Among HCM patients, malignant ventricular arrhythmias were observed in four patients, five qualified for an ICD implantation, and one qualified for a heart transplant. In the LVNC group, one patient was qualified for a heart transplant. Atrial flutter and atrial fibrillation were not observed in any of the patients, and one of the patients with HCM had a previous history of supraventricular tachycardia.

Significant differences in terms of the QRS-T angle were observed among cardiomyopathy patients with and without the end point of the study (MACE) (Table 2). QRS-T angle was greater among patients with unfavorable outcomes, independent of whether the outcome was an arrhythmic event or heart failure progression (Table 2). In terms of other ECG parameters, greater PQ, QRS, and QTc intervals as well as two or more negative T waves were observed more frequently among patients with MACE than in those who did not meet the end point of the study.

Serum biomarker concentrations of NT-proBNP were significantly higher among patients with MACE (median 3262 vs. 69 ng/mL, $p < 0.0001$). Similarly, NYHA or Ross scale classes were significantly greater among patients with MACE ($p < 0.001$) than in cardiomyopathy patients without adverse outcomes.

Table 2. QRS-T angle in cardiomyopathy patients according to the adverse outcome.

	QRS-T Angle		
	No End Point	**Met End Point**	***p*-Value**
VT	70.1° ± 31.8°	137.2° ± 25.3°	<0.001
ICD	72.5° ± 34.5°	135.6° ± 24.2°	<0.001
HTx	74.7° ± 36.6°	133.7° ± 22.8°	<0.001
All end points	64.7° ± 28°	133.2° ± 23°	<0.001

Data are given as mean and standard deviation, VT—ventricular tachycardia, ICD—implantable cardioverter defibrillator inserted/qualified for insertion, HTx—qualification for heart transplant.

In the random forest model, the parameters associated the strongest with adverse outcomes in children with cardiomyopathies were QRS-T angle, NT-proBNP, NYHA or Ross class, and pathological T wave inversions in one or more leads with 92% specificity and 82% sensitivity (Figure S1, Table S2 Supplementary Materials). On Kaplan–Meier curves reduced survival was associated with a QRS-T angle > 120°, greater NYHA class, and abnormal NT-proBNP and troponin I levels (Figure 1).

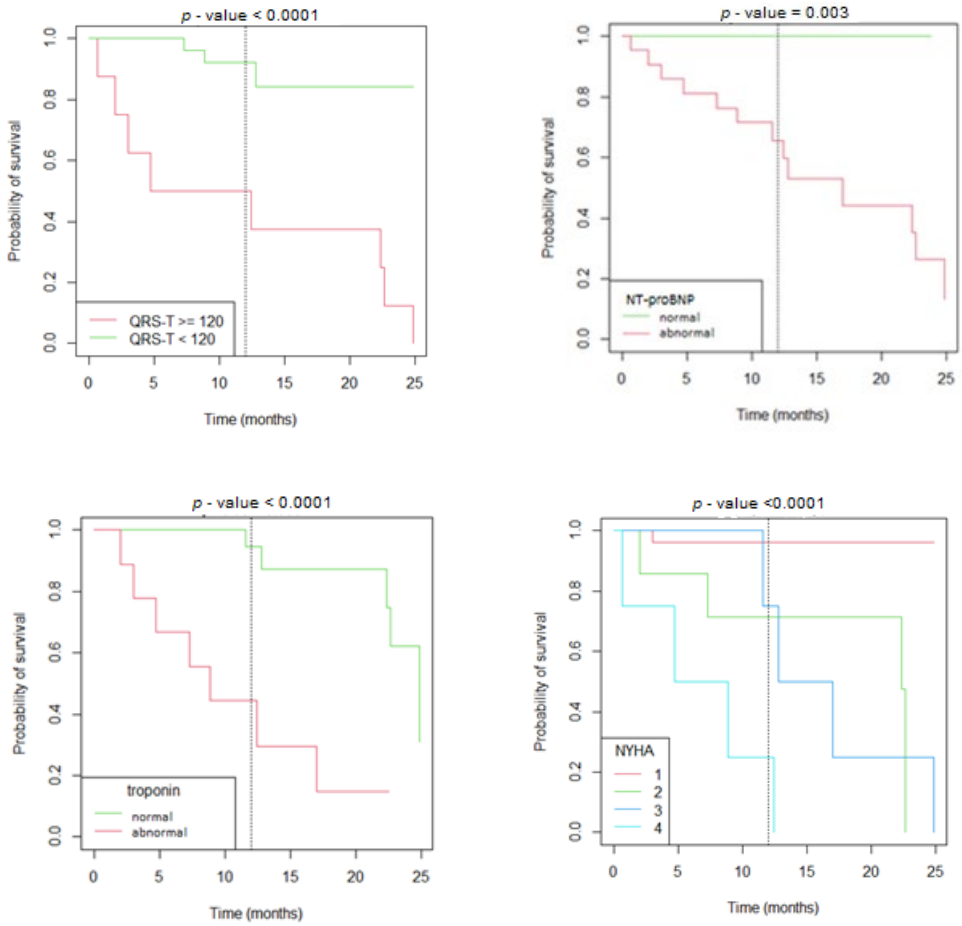


Figure 1. Kaplan–Meier survival curves according to the value of the QRS-T angle, serum concentrations of NT-proBNP and troponin, and NYHA/Ross scale.

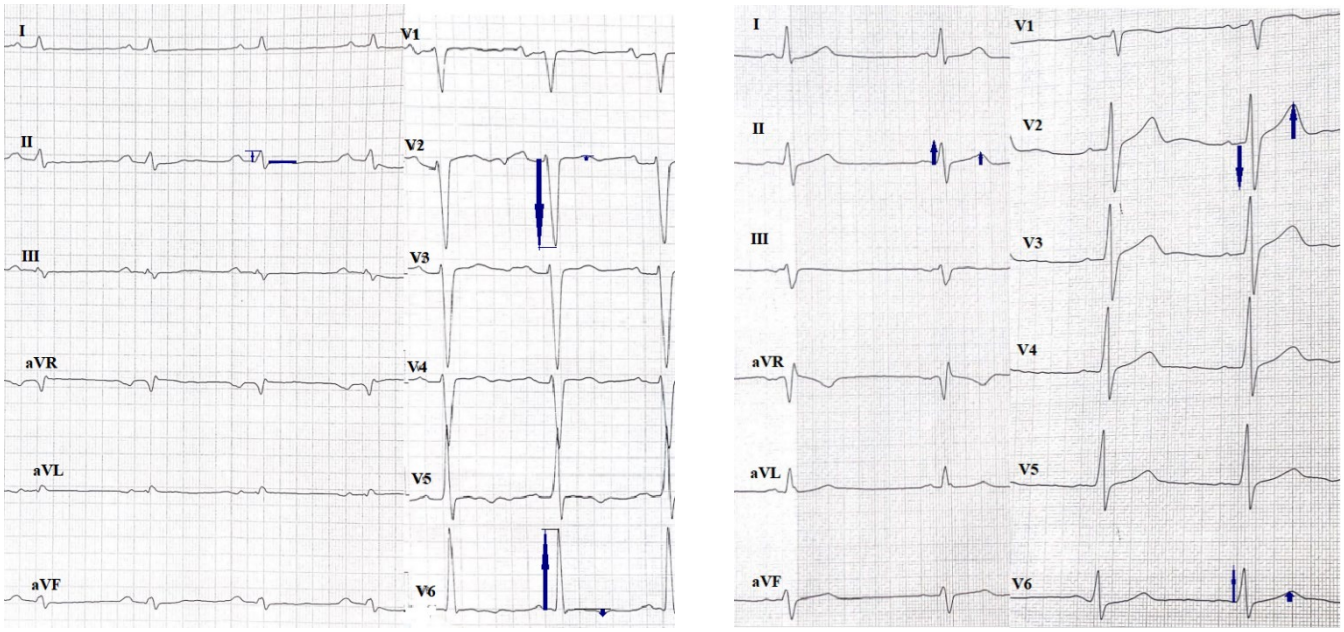
3.1. Dilated Cardiomyopathy

In the DCM group, the QRS-T angle was significantly greater among patients with unfavorable outcomes (134° vs. 48°, $p < 0.001$) (Table 3); greater QRS-T angle was also observed among DCM patients with malignant arrhythmia ($p < 0.001$) (Table S4 Supplementary Materials) and qualified for a heart transplant ($p < 0.001$) independently. The differences between an ECG with a normal and an abnormal spatial QRS-T angle can be observed in Figure 2.

Table 3. Parameters associated with adverse outcomes in patients with DCM.

	DCM no MACE $n = 13$	DCM MACE $n = 6$	p-Value
HR (bpm)	88 (82–100)	100 (74–137)	0.759
PQ (ms)	123.8 ± 18.5	140.0 ± 28.9	0.157
QRS (ms)	76.2 ± 10.4	85.0 ± 18.7	0.317
QTc (ms)	392.9 ± 31.4	431.1 ± 38.9	**0.035**
QRS-T (degrees)	48.2 ± 22.9	133.7 ± 22.8	**<0.001**
Negative T-waves ≥ 2 leads	0	4 (66%)	**0.007**
NT-proBNP (pg/mL)	58 (37–146)	3068 (2123–3810)	**<0.001**
Troponin (ng/mL)	2.7 (1.5–9.5)	48.9 (25.9–95.4)	**0.013**
NYHA/Ross (I/II/III/IV)	13 (100%)/0/0/0	0/1 (17%)/1 (17%)/4 (66%)	**<0.001**
LVEF %	44.4 ± 6.78	21.9 ± 5.78	**<0.001**
LVIDd z-score	2.86 ± 0.87	5.50 ± 0.77	**<0.001**
LVPWD z-score	0.33 ± 0.493	1.07 ± 0.66	**0.042**

n number of patients, DCM—dilated cardiomyopathy, MACE—major adverse cardiac event, HR heart rate (in beats per minute), ms—milliseconds, LVEF—left ventricular ejection fraction, LVIDd—left ventricular internal diastolic diameter, LVPWd left ventricular posterior wall thickness in diastole.



(**a**) (**b**)

Figure 2. ECGs of patients with DCM with (**a**) an abnormal QRS-T angle of 164° and (**b**) a normal QRS-T angle of 88°.

Other ECG parameters associated with MACE were greater QTc interval and two or more pathological negative T waves (Table 3). There were no significant differences in terms of PQ interval or QRS duration. There were no significant differences in the ECG parameters (including QRS-T angle) between children with DCM who did not present with MACE and the control group (mean QRS-T 48° vs. 41°, $p = 0.37$). Children with DCM who experienced MACE had significantly greater QRS-T angle, longer QTc interval, and ≥2 pathological negative T waves on their baseline ECG in comparison with the control group (Table S3 Supplementary Materials).

Concentrations of serum biomarkers (NT-proBNP and troponin) were significantly higher among DCM patients with MACE compared to children with DCM without MACE (NT-proBNP median 3068 vs. 58 pg/mL, troponin median 49 vs. 3 ng/mL) (Table 3). A

moderate correlation was observed between QRS-T angle and NT-proBNP (r = 0.55); no significant correlation was found between QRS-T angle and troponin levels.

In echocardiography, greater LVIDd *z*-scores as well as lower LVPWd *z*-scores and LVEF were observed among patients with unfavorable outcomes (Table 3). A strong positive correlation was observed between LVIDd *z*-score and QRS-T angle (r = 0.72), as well as a moderate correlation between decreased LVEF and greater QRS-T angle (r = −0.69). No significant correlation was found between LVPWd and QRS-T angle.

In patients with DCM and ventricular tachycardia, a greater QRS duration (85° vs. 70° ms), QRS-T angle (142° vs. 57°), PQ interval (153 vs. 123 ms), and ≥2 pathological negative T waves were observed in comparison with children with DCM without ventricular arrhythmia (Table S4 Supplementary Materials). NT-proBNP was also significantly higher among these patients (2232 vs. 69 pg/mL); however, there were no significant differences in terms of troponin levels (Table S4 Supplementary Materials). Patients with DCM with heart failure end point showed the same risk factors associated with unfavorable outcomes as those with MACE.

The random forest model indicated that the best predictors for MACE among DCM patients were LVEF, NT-proBNP, NYHA/Ross scale, LVIDd z-score, and QRS-T angle.

3.2. Hypertrophic Cardiomyopathy

In HCM patients, a greater QRS-T angle was observed in patients with MACE compared to patients without adverse outcomes (133° vs. 85°; $p = 0.004$) (Table 4). HCM patients with MACE had also a greater PQ interval (140 vs. 120 ms, $p = 0.02$) and QRS duration (105 vs. 70 ms, $p = 0.002$), and more frequent presence of two or more pathological negative T waves ($p = 0.01$) (Table 4).

Table 4. Parameters associated with adverse outcomes in children with HCM.

	HCM no MACE ***n* = 11**	**HCM MACE** ***n* = 6**	***p*-Value**
HR (bpm)	97.4 ± 26.98	73.8 ± 17.72	**0.048**
PQ (ms)	120 (120–135)	140 (140–163)	**0.021**
QRS (ms)	70 (70–70)	105 (85–118)	**0.002**
QTc (ms)	406.9 ± 27.46	433.6 ± 34.32	0.1
QRS-T (degrees)	84.6 ± 25.69	132.5 ± 26	**0.004**
Negative T-waves ≥ 2 leads	2 (18%)	5 (100%)	**0.012**
ST elevation	0	3 (50%)	0.055
ST depression	1 (9%)	3 (50%)	0.193
LVH	0 (0%)	5 (83%)	0.416
NT-proBNP (pg/mL)	124.5 (45–908)	2659 (1611–4894)	**0.011**
Troponin (ng/mL)	8.7 (1.5–26.4)	50.1 (24.4–131.1)	0.06
NYHA/Ross (I/II/III/IV)	8 (73%)/3 (27%)/0/0	1 (17%)/3 (50%)/2 (33%)/0	**0.038**
LVEF %	61.9 ± 6.73	51.7 ± 19.01	0.253
LVIDD *z*-score	−1.87 ± 1.576	−1.74 ± 2.471	0.909
LVPWD *z*-score	2.90 (2.15–4.1)	6.40 (2.85–10.25)	0.191
IVSd *z*-score	7.4 ± 4.4	12.6 ± 4.7	0.052

n number of patients, HCM hypertrophic cardiomyopathy, MACE—major adverse cardiac event, HR heart rate (in beats per minute), LVEF- left ventricular ejection fraction, LVIDd—left ventricular internal diastolic diameter, LVPWd—left ventricular posterior wall thickness in diastole, IVSd—interventricular septum in diastole, LVH—left ventricular hypertrophy.

In comparison with the control group, patients with HCM had a greater QRS-T angle (100° vs. 41°, $p < 0.001$), QTc interval (420 vs. 380 ms, $p = 0.002$), as well as more frequent presence of at least two pathological T-wave inversions ($p = 0.005$). No differences were observed between the HCM group and the control group in terms of heart rate and, durations of PQ or QRS intervals.

Serum concentrations of NT-proBNP were significantly higher among HCM patients with MACE compared to patients without adverse events (2659 vs. 125 pg/mL, $p = 0.01$); the difference in the troponin levels between the two groups was borderline significant

(p = 0.06) (Table 4). Similarly to DCM patients, higher NYHA or Ross scale was observed among patients with MACE (p = 0.038). On correlation analysis, a correlation between NYHA scale and QRS-T angle (r = 0.5) was found, but no significant correlation was found between QRS-T angle and NT-proBNP.

In echocardiography, the IVSd z-score was borderline significant in MACE patients (p = 0.052). In HCM patients with MACE, there were no significant differences in terms of LVEF or LVIDd in comparison with patients without adverse events.

In HCM patients with ventricular arrhythmia, greater QRS-duration, QRS-T angle and more than two pathological negative T waves were present more frequently in comparison with patients without arrhythmia (Table S5 Supplementary Materials). There were no significant differences in terms of NT-proBNP and troponin levels between HCM patients with and without ventricular tachycardia (Table S5 Supplementary Materials).

The random forest model showed that QRS, QRS-T angle, LVH and PQ were the best predictors for MACE among HCM patients.

Inter-observer variability according to Lin's concordance correlation coefficient in terms of QRS-T angle description was 0.99 [CI 0.98; 0.99].

4. Discussion

In the present study, we outlined electrocardiographic risk factors associated with unfavorable outcomes among patients with cardiomyopathies. In adults with both dilated and hypertrophic cardiomyopathy, a greater QRS-T angle has been associated with unfavorable outcomes [2–4,6]. Similarly, in our study we observed a significantly greater QRS-T angle in patients with MACE, independently of the type of cardiomyopathy. Furthermore, increased QRS-T angle was observed in both heart failure and arrhythmic event groups. The random forest model outlined QRS-T angle as a leading factor in predicting MACE in all cardiomyopathy patients as well as HCM and DCM independently. Kaplan–Meier survival analysis showed that a QRS-T angle >120° was associated with an unfavorable outcome. This suggests that the spatial QRS-T angle could be a helpful parameter in assessing the risk for disease in different types of cardiomyopathies. It appears that the conduction abnormalities on the myocyte level, independently of the cardiomyopathy type, are reflected through the QRS-T angle.

4.1. Dilated Cardiomyopathy

In our study, increased QRS-T angle and QTc, as well as the presence of at least two pathologically inverted T waves were associated with MACE in children with DCM. In the scarce studies on children, QTc has been associated with unfavorable outcomes. Chen et al. found a relationship between increased risk of malignant arrhythmia and: longer QRS duration, abnormal T-waves, ST-segment depression, QTc, JTc intervals, and QT and JT dispersion [23]. Similarly, Ture et al. suggested a greater QT interval as well as QT and T-wave peak-end dispersion in children with dilated cardiomyopathy who died [24]. However, none of these studies analyzed the association between the QRS-T angle or $\geq$2 pathologic negative T-waves and adverse outcomes in children.

In adult patients with idiopathic dilated cardiomyopathy, a relationship between greater QRS-T angle and mortality, risk of an ICD shock or rehospitalization due to heart failure had been observed, with cut-off values ranging between >90° and 152° [2–4]. In our cohort, we observed a mean spatial QRS-T angle of 133° among patients with adverse outcomes, which seems to be in agreement with adult reports. The QRS-T angle seems to be a useful parameter in identifying DCM children with the greatest cardiovascular risk, but further studies on a larger number of patients are necessary to confirm our finding.

In contrast to the study by Chen et al., we found no correlation between pathological T wave inversion in only one ECG lead and adverse outcomes [23]. In our study, at least two negative T waves were associated with MACE. This seems to support the role of the spatial QRS-T angle, because its calculation includes the magnitude of the T-wave in three

leads. Thus, pathological inversion of two or more T-waves on a 12-lead ECG could be more specific in identifying patients at greatest risk.

Meulen et al. reported that the serum biomarker NT-proBNP is associated with adverse outcomes in children with dilated cardiomyopathy [25]. A similar observation was made in our study. We found a positive correlation between serum concentrations of NT-proBNP and greater QRS-T angle, which suggests an association between heart failure severity and abnormalities in 12-lead ECG. Troponin I levels were also significantly higher in children with DCM and adverse outcomes, which might indicate another serum biomarker useful in risk stratification. To our knowledge, troponin I levels have not been analyzed previously in the pediatric DCM population. In adults with idiopathic dilated cardiomyopathy, it has been reported that increased NT-proBNP, troponin I, and troponin T levels are associated with increased mortality [26–28]. Furthermore, in adults with LMNA mutations, both increased troponin T and NT-proBNP were associated with the presence of malignant arrhythmias [29].

Unsurprisingly, echocardiographic findings such as decreased left ventricular ejection fraction, shortening fraction and increased left ventricular end diastolic dimension have been associated with increased risk of mortality in pediatric dilated cardiomyopathy patients [24,25,30]. In our study, similar observations were made; decreased LVEF and LVPWd, and increased LVIDd *z*-scores were associated with unfavorable outcomes. Correlations between QRS-T angle and echocardiographic parameters such as LVIDd and LVEF were also shown, suggesting that electrocardiographic changes reflect echocardiographic abnormalities and could be helpful in predicting adverse outcomes.

4.2. Hypertrophic Cardiomyopathy

Ninety-seven per cent of pediatric HCM patients have abnormalities in their ECG [31]. However, in a multicenter study by Norrish et al. none of the proposed electrocardiographic parameters adequately predicted the risk of malignant arrhythmia in children with HCM [31]. However, in the study by Norrish et al. neither the QRS-T angle nor multiple pathological T waves have been analyzed as parameters associated with unfavorable outcome. In our study, children with ventricular arrhythmias had a significantly greater QRS interval and QRS-T angle (133° vs. 89°), and two or more pathological negative T waves on their baseline ECG, in comparison with children with HCM without ventricular tachycardia. This seems to be in agreement with the study by Cortez et al. on children and adolescents up to 23 years old, in whom spatial QRS-T angle > 124° had a high negative predictive value for excluding risk of ventricular arrhythmias [14]. Thus, both QRS-T angle and multiple negative T wave inversions in ECG might be helpful in identifying patients at greatest risk of adverse outcomes in the pediatric population; these have not been analyzed in larger pediatric cohorts.

Interestingly, patients with HCM with no MACE also had a significantly greater QRS-T angle than the control group. This is in agreement with a study by Cortez et al. on adults, in which greater QRS-T angle helped to identify patients with HCM [32]. It seems that the QRS-T angle might be helpful in differentiating HCM patients from healthy individuals both in the adult and pediatric populations. Furthermore, because the greatest QRS-T angle was observed among patients with HCM and MACE, regular QRS-T measurements could help to assess the disease's progression. However, further studies on a larger number of patients are necessary to confirm this hypothesis.

In terms of serum biomarkers, the serum concentration of NT-proBNP was significantly higher among HCM patients with adverse outcomes (2659 vs. 125 pg/mL). This corresponds to the findings by Kaski et al., who showed a relationship between increased NT-proBNP levels and HCM severity among pediatric HCM patients [33]. Thus, we did not find a relationship between malignant arrhythmia occurrence and NT-proBNP in HCM children. This suggests that NT-proBNP may be useful in outlying patients with heart failure progression but not necessarily in those with greatest risk of ventricular arrhythmias.

A similar observation was made in an adult study by Coates et al., in which elevated NT-proBNP was a predictor of heart failure death but not of sudden cardiac death [34].

CMR plays a significant role in the diagnosis of hypertrophic cardiomyopathy as well as identifying the extent of myocardial fibrosis [35]. Increased troponin I and T levels were associated with adverse cardiovascular events and increased fibrosis on CMR [36,37]. In our study, troponin I levels among HCM patients who had MACE were borderline significant ($p = 0.06$) in comparison with the group without MACE. This may be explained by the fact that the majority of patients with adverse outcomes had arrhythmia and the number of patients who presented with heart failure in this group was low. Increased troponin concentration might be associated more with heart failure progression than with arrhythmia. However, further studies on a larger number of patients are necessary to support this hypothesis.

Correlation analysis in the DCM group showed an association between the QRS-T angle and NT-proBNP as well as QRS-T angle and echocardiographic parameters such as LVEF or LVIDd z-score. Thus, in patients with HCM, even though the QRS-T angle was greater among patients with MACE, no correlations between echocardiographic parameters or serum biomarkers were found. Therefore, the QRS-T angle seems to be a valuable parameter in assessing conduction abnormalities, despite their heterogeneous origin. It appears that an increased QRS-T angle may reflect both abnormal stretching of the myocytes and irreversible changes in the myocardium such as fibrosis. On one hand, Li et al. reported in adults a decrease in the QRS-T angle after medical treatment [4], suggesting that some of the myocardial depolarization and repolarization abnormalities may be reversible. On the other hand, Jensen et al. showed a correlation between the QRS-T angle and late gadolinium enhancement on CMR in patients with HCM [38]. This proves that the QRS-T angle is also abnormal in patients with irreversible myocardial changes such as fibrosis. Taking into account the association between QRS-T angle and MACE, it would be worth exploring whether ECG changes precede fibrosis in CMR. Furthermore, in adult patients with HCM it was noted that genotype-positive patients tend to have a greater QRS-T angle than genotype negative patients [32]. Thus, depolarization abnormalities may be associated with the type of genetic mutation. Future studies on a larger population are necessary to approach these questions.

Some limitations of the study can be outlined. Because this was a single-center study and the prevalence of cardiomyopathies in children is low, the included number of patients was limited. Thus, we encourage studies on a larger scale, because the QRS-T angle seems to be an easily obtainable but not well-explored parameter in the pediatric population.

5. Conclusions

QRS-T angle appears to be a valuable addition to standard electrocardiogram (ECG) interpretation. It is associated with adverse outcomes in children with both dilated and hypertrophic cardiomyopathies. Furthermore, serum biomarkers such as troponin and NT-proBNP might also be useful in outlining patients at the highest risk of heart failure progression and death.

Supplementary Materials: The following supporting information can be downloaded at: https://www.mdpi.com/article/10.3390/jcm11236930/s1, Table S1: Differences in the baseline ECG, echocardiographic parameters, adverse events occurrence among HCM, DCM and LVNC patients; Table S2: Random forest regression model in children with cardiomyopathies—specificity and sensitivity; Figure S1. Random forest model presenting variables associated with unfavorable outcomes in children with cardiomyopathies; Table S3: Comparison between DCM patients with MACE and control group; Table S4: Comparison between DCM patients with and without ventricular tachycardia; Table S5: Comparison between HCM patients with and without ventricular tachycardia.

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Informed Consent Statement: Informed consent was obtained from all subjects/subjects guardians involved in the study.

Conflicts of Interest: The authors declare no conflict of interest.

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Abnormal left atrial strain and left atrial stiffness index are associated with adverse outcomes in children with cardiomyopathies: a pilot study

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Abnormal left atrial strain and left atrial stiffness index are associated with adverse outcomes in children with cardiomyopathies: a pilot study

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Conventional diastolic dysfunction parameters seem to be imperfect when applied to the pediatric cardiomyopathy population. The aim of this pilot study was to search for novel echocardiographic parameters associated with adverse outcomes in children with the most common cardiomyopathies. Fifty-six patients with pediatric cardiomyopathies (28 with dilated, 21 with hypertrophic, 7 with left ventricular non-compaction cardiomyopathy) and 28 healthy subjects were included in the study. Left atrial reservoir (LASr), conduit (LAScd) and contraction (LASct) strain, left atrial stiffness index (LASI), as well as conventional diastolic dysfunction parameters were measured using echocardiography. Adverse outcomes were defined as heart failure (including heart transplant) and arrhythmic endpoints. Patients with adverse outcomes presented with significantly lower LASr (16.68% ± 8.64% vs. 33.97% ± 9.99%, p-value < 0.001), lower LAScd (− 10.37% ± 5.83% vs. − 25.50% ± 9.24%, p-value < 0.001) and higher values of LASI (0.69 [IQR 0.34; 1.11] vs. 0.21 [IQR 0.16; 0.31], p-value < 0.001). LASr < 20%, LAScd ≥ − 12%, and LASI ≥ 0.26 were all associated with reduced survival. LASr, LAScd and LASI seem to be promising parameters in predicting adverse outcomes in the most common pediatric cardiomyopathies. Left atrial strain parameters and LASI are helpful in differentiating healthy control subjects from children with hypertrophic and dilated cardiomyopathies.

Conventional echocardiographic ventricular diastolic dysfunction assessment is not perfect in pediatric patients with cardiomyopathies due to variability of the measured parameters with age, difficulty in discriminating cardiomyopathy patients from healthy subjects as well as poor interobserver agreement[1]. Furthermore, some diastolic function parameters may lengthen or shorten depending on the severity of the ventricular stiffness. For instance, mitral valve deceleration time may lengthen in the early diastolic dysfunction stages but shorten with the progression of the disease. Thus, the search for new, easily obtainable, and more objective parameters is necessary in the pediatric population.

Left atrial strain has recently received attention in adult studies on various cardiomyopathy types[2–7]. Left atrial strain measurements reflect both the systolic and diastolic function of the ventricle, while being influenced by the ventricle's contractility, relaxation, compliance, and intra-ventricular pressures. Atrial filling and emptying abnormalities are dependent on the ventricular conditions. Atrial wall deformation measured by strain may be more accurate in describing ventricular diastolic dysfunction in the pediatric population compared to conventionally measured inflow and annular movement velocities, especially when taking into account the variability of the latter with age.

Because left atrial strain is an easily obtainable and reproducible parameter helpful in outlining adult cardiomyopathy patients at greatest cardiovascular risk, it appears to be worthy of attention also in children[8,9]. There are scarce studies concerning left atrial strain in pediatric cardiomyopathies[10–12]. To our knowledge, no studies concerning the association between left atrial strain and survival in pediatric cardiomyopathies have been published so far. Thus, the aim of our prospective pilot study was to assess the value of left atrial strain in predicting

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adverse events in children with the 3 most common types of cardiomyopathies: dilated, hypertrophic and left ventricular non-compaction. Furthermore, we aimed at outlining whether left atrial strain parameters differ between healthy subjects and patients with early stages of cardiomyopathies.

Methods

Patients with dilated, hypertrophic, and left-ventricular non-compaction cardiomyopathies were recruited from the Department of Pediatric Cardiology and General Pediatrics between 2020 and 2023. The diagnosis was based on echocardiography; hypertrophic cardiomyopathy was defined as left ventricular wall thickness *z*-score > 2 measured in diastole; dilated cardiomyopathy as left ventricular internal end-diastolic dimension (LVIDd) *z*-score > 2 with concomitant reduced ejection fraction, and left ventricular non-compaction according to the Jenni et al. criteria with non-compaction to compaction (NC:C) ratio in systole > 2:1[13–15]. When borderline cases were present, diagnosis was confirmed using cardiac magnetic resonance (CMR) imaging. Children aged 0–18 years were included in the pilot study.

The exclusion criteria included the following: co-existing co-morbidities including genetic syndromes co-existing with cardiomyopathies (i.e. Noonan syndrome, myopathies, metabolic diseases), ventricular hypertrophy or dilatation due to secondary reasons (i.e. congenital heart defects, hypertension), and lack of consent for participation in the study.

The control group consisted of healthy age- and sex-matched children. They were either recruited from the daily clinic, where they appeared due to a benign heart murmur, or from schools. Two patients from the control group were excluded from the analysis because of newly diagnosed ventricular arrhythmia.

Each patient had an ECG, echocardiography, and ECG Holter monitoring performed at the baseline visit. Moreover, among children with cardiomyopathies serum biomarkers N-Terminal prohormone of Brain Natriuretic Peptide (Nt-proBNP) and high-sensitivity troponin I were additionally analyzed. The medication and family history of each patient was recorded. Previous medical history for malignant arrhythmia (defined as ventricular tachycardia) was evaluated. Heart failure symptoms were assessed using NYHA or Ross scale in younger children[16]. If available, genetic test results were reported; the majority had a TruSight Cardio Sequencing Panel, while in a few patients with familial genotype Sanger sequencing was performed.

Unfavorable outcome were defined as follows: malignant arrhythmia (non-sustained ventricular arrhythmia (nsVT), sustained ventricular arrhythmia (sVT), ventricular fibrillation (VF)), listing for heart transplant, ICD implantation or appropriate ICD shock, and cardiac death. The arrhythmic endpoint included the presence of malignant arrhythmia, qualification for ICD implantation, or sudden cardiac death. The heart failure endpoint was defined as listing for heart transplant, undergoing heart transplant, or death due to heat failure.

This prospective study was approved by the local University Bioethics Committee. The study was performed in accordance with relevant guidelines and regulations (including Declaration of Helsinki and STROBE guidelines). Prior to participating in the study, all participants' legal guardians as well as children ≥ 16 years signed a written informed consent form.

Echocardiography

Echocardiography was performed using Phillips EPIQ ultrasound system 9.0.1 with X5-1, S5-2 and S8-3 transducers. In each patient left ventricular ejection fraction (LVEF) was recorded using the Simpson biplane method. The left ventricular measurements such as: left ventricular internal diastolic dimension (LVIDd), left ventricular posterior wall thickness in diastole (LVPWd), and interventricular septum thickness in diastole (IVSd) were acquired using M-mode. *Z*-scores were used to account for the differences between the patients' height and weight[17].

Diastolic function was assessed using both pulsed-wave Doppler and tissue Doppler velocities (TDI). Mitral inflow peak E-wave, A-wave velocities and mitral E-wave deceleration time (DT) were measured. In TDI medial (septal) and lateral early (e′) and late (a′) mitral annulus velocities as well as isovolumetric relaxation time (IVRT) were assessed[18]. The left atrial volume was measured using the area-length approximation using the 4-chamber and 2-chamber views and corrected for body surface area (LAVi left atrial volume index)[19]. Mitral valve regurgitation (MR) was graded from 0 to 4[20].

Myocardial strains were acquired using speckle tracking echocardiography with Philips software. Left ventricular global longitudinal strain (LV GLS) was obtained from the 4-chamber, 3-chamber, and 2-chamber views. Atrial strain was obtained from the 4-chamber view using ventricular end diastole as the zero reference point in accordance with the current recommendations[21]. Left atrial strain during the reservoir (LASr), conduit (LAScd) and contraction phases (LASct) were recorded. Non-invasive left atrial stiffness index (LASI) was defined as the ratio between average E/e′ to LASr[22]. 20% of randomly selected studies of cardiomyopathies patients were reanalyzed by a second observer to look for inter-observer variability in terms of differences in left atrial strain.

Statistical analysis

Statistical analysis was performed using Statistica 13.3 version and R version 4.2.2 GNU General Public License. Continuous data are presented as mean and standard deviation (SD) or median and first and third quartile (IQR), depending on the distribution. Categorical variables were compared using the test for equality of proportions. For continuous variables *t*-test, Mann–Whitney *U* test, F test and Kruskal–Wallis test were used depending on the number and distribution of the compared variables. Correlation analysis was performed using Pearson's or Spearman's correlations depending on the distribution. Random forest model was used to define the echocardiographic parameters that were most helpful in outlining patients with adverse outcomes in the whole cardiomyopathy group, as well as in dilated and hypertrophic cardiomyopathy subgroups. Kaplan–Meier survival curves were used for survival assessment in the whole cardiomyopathy group. This analysis was not performed on the

subgroups due to a limited number of patients. Inter-observer variability was calculated using Lin's concordance correlation coefficient. A p-value < 0.05 was considered statistically significant.

Conference presentation

Part of the results concerning DCM were presented at the 56th Annual Meeting of the Association for European Paediatric and Congenital Cardiology.

Results

A total of 84 patients was included in the study, 28 with DCM, 21 with HCM, **7** with LVNC, and 28 in the control group. The median age was 8 years (IQR 3; 14). The median observation time of cardiomyopathy patients was 270 days (IQR 158; 525 days). The baseline characteristics of patients with cardiomyopathies and the control group are presented in Table 1. There were no significant differences between the cardiomyopathy groups and the control group in terms of age, sex, BMI, or heart rate (Table 1). Baseline echocardiographic parameters in the 3 cardiomyopathy subgroups are presented in Table S1 (Supplementary Materials). DCM group was characterized by reduced LVEF (40.68% [IQR 30.53; 45.95]) and enlarged left ventricle (LVIDd z-score: + 3.74 ± 1.42). In the HCM group hypertrophy of the ventricular septum and left ventricular wall (IVSd z-score + 5.40 [IQR 3.02; 11.30]; LVPWd z-score + 3.08 [IQR 1.74; 5.30]), as well as increased maximal LVOT pressure gradient (9 mmHg [IQR 6; 17]) were present. In the LVNC group the median LVEF was 56.7% (IQR 55.1; 58.3). The 3 cardiomyopathy groups differed only in terms of only some of the diastolic function parameters (Table S1, Supplementary Materials). There were no significant differences in LASr, LAScd, LASI, or LAVi between the 3 groups; LASct was borderline significant (p-value 0.049).

Altogether, 29% of patients (16/56) experienced adverse outcomes, 7 (25%) in the DCM group, 7 (33%) in the HCM group and 2 (29%) in the LVNC group. Among all cardiomyopathy patients 9 (16%) experienced a heart failure endpoint, whereas 12 (21%) experienced an arrhythmic endpoint. During the observation time 9 children were listed for heart transplant.

Eighteen patients (32%) had a positive family history of cardiomyopathies, 6 of whom experienced an adverse outcome. There was no statistically significant difference in terms of positive family history between patients with and without adverse outcomes ($p = 0.59$). Genetic testing was performed in 43 patients (78%): in 15 (27%) the panel was positive, in 13 (23%) a variant of uncertain significance was found, in 2 the results were not available yet, and 13 (23%) had a negative panel.

Patients with cardiomyopathies and adverse outcomes had significantly lower LASr (16.68% ± 8.64% vs. 33.97% ± 9.99%), less negative LAScd (− 10.37% ± 5.83% vs. − 25.50% ± 9.24%) and greater LASI (0.69 [IQR 0.34; 1.11] vs. 0.21 [IQR 0.16; 0.31]) when compared to cardiomyopathy patients without adverse outcomes (Table 2). In terms of other echocardiographic parameters, patients with adverse outcomes had significantly greater LAVi,

	DCM $n = 28$	HCM $n = 21$	LVNC $n = 7$	CTRL $n = 28$	p-value
Age (years)	8 (2.08; 14.0)	6.5 (0.5–15)	11.0 (9.0; 15.0)	7 (3.5; 13.5)	0.332
Sex (F/M)	11/17	8/13	6/1	11/17	0.125
BMI (kg/m^2)	15.96 (13.47; 19.91)	19.61 (15.61; 23.56)	15.42 (13.91; 16.74)	17.13 (15.29; 19.49)	0.065
Heart rate (bpm)	91.58 (77.43; 109.45)	80 (70.0; 96.62)	83.80 (59.94; 110.0)	85.59 (73.91; 102.13)	0.355
Observation time (days)	226.50 (148.5; 379)	447 (166; 637)	168 (436; 441)	x	0.316
Medication (Y/N)	28/0	17/4	5/2	x	**0.027**

Table 1. Baseline characteristics of patients with cardiomyopathies and the control group. Data are presented as median and (IQR) or number of patients. *BMI* body mass index, *bpm* beats per minute, *CTRL* control group, *DCM* dilated cardiomyopathy, *F* female, *HCM* hypertrophic cardiomyopathy, *LVNC* left ventricular non-compaction, *M* male, *n* number of patients, nN no,Y yes. Significant values are in bold.

	LASr [%]			LAScd [%]			LASI		
	End-point	No end-point	p-value	End-point	No end-point	p-value	End-point	No end-point	p-value
HF endpoint	11.54 ± 6.31	32.38 ± 10.25	< **0.001**	− 7.39 ± 4.45	− 23.82 ± 9.62	< **0.001**	0.92 (0.57; 2.09)	0.24 (0.18; 0.38)	< **0.001**
Arrhythmia endpoint	18.39 ± 8.56	31.93 ± 11.71	< **0.001**	− 11.20 ± 6.24	− 23.90 ± 10.24	< **0.001**	0.60 (0.37; 1.10)	0.23 (0.18; 0.37)	< **0.001**
All endpoint	16.68 ± 8.64	33.97 ± 9.99	< **0.001**	− 10.37 ± 5.83	− 25.50 ± 9.24	< **0.001**	0.69 (0.34; 1.11)	0.21 (0.16; 0.31)	< **0.001**

Table 2. Differences in left atrial reservoir strain, left atrial conduit strain and left atrial stiffness index between cardiomyopathy patients with and without adverse outcomes. Data are presented as mean and ± standard deviation or median and (inter-quartile range) depending on the variables' distribution. *HF* heart failure, *LASct* left atrial conduit strain, *LASI* left atrial stiffness index, *LASr* left atrial reservoir strain. Significant values are in bold.

lower LVEF, lower E, A, average e′ wave velocities, and greater E/A ratio and lateral IVRT (Table S2, Supplementary Materials). There were no significant differences in terms of LASct, MR, and some of the diastolic function parameters (DT, a′, medial and lateral e′/a′, medial IVRT, average E/e′).

When applying the random forest model to assess echocardiographic parameters most helpful in predicting adverse outcomes LAScd, LASr and LASI were among the top 3 variables, with the model having a 50% sensitivity, 100% specificity, 100% positive predictive value and 90% negative predictive value (Fig. F1, Supplementary Materials). On Kaplan–Meier survival curves LASr < 20%, LAScd ≥ − 12%, and LASI ≥ 0.26 were all associated with reduced survival in patients with cardiomyopathies (Figs. 1, 2, 3).

Dilated cardiomyopathy

There were 28 children with dilated cardiomyopathy, 7 of whom (33%) experienced an adverse outcome (4 had an arrhythmic event, 7 heart failure adverse outcome). The differences between DCM patients with and without adverse outcomes are presented in Table 3. Patients with adverse outcomes had significantly greater NT-proBNP serum concentrations than those without, as well as greater NYHA or Ross scale score.

In terms of echocardiographic parameters, patients with adverse outcomes had significantly lower LASr, less negative LAScd and greater LASI (Table 3). They presented with significantly lower LV GLS, and LVEF, as well as greater LVIDd *z*-scores. There were significant differences only in some of the diastolic function parameters between the 2 groups (lower A-wave velocity, greater E/A ratio, lower e′, lateral a′, greater IVRT lateral). However, there were no significant differences in terms of LASct, LAVi, MR and some diastolic dysfunction parameters, such as E-wave velocity, DT, medial IVRT, medial a′, medial and lateral e′/a′ and average E/e′.

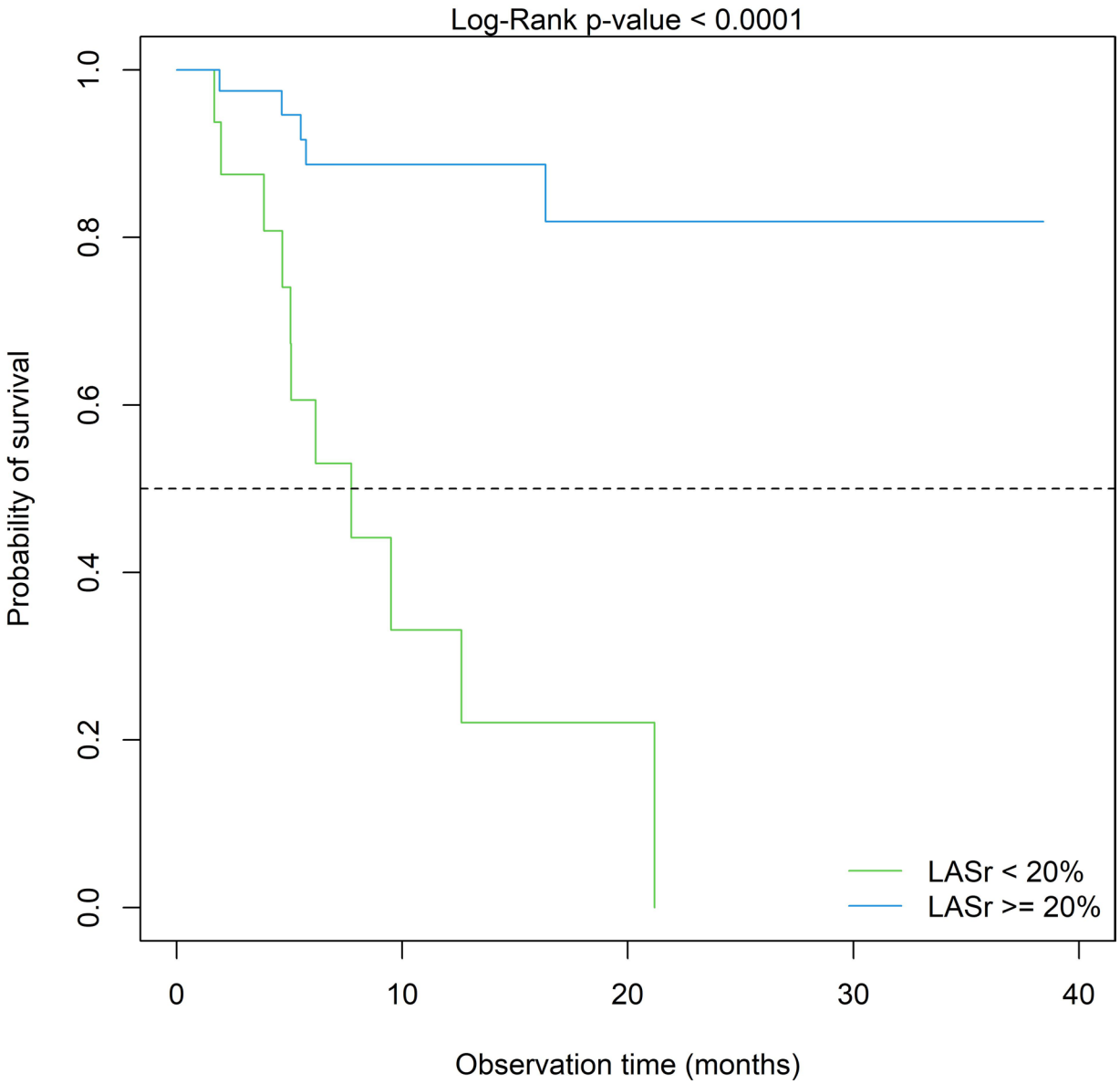

Fig. 1. Kaplan–Meier survival curves in cardiomyopathy patients with different left atrial reservoir strain (LASr).

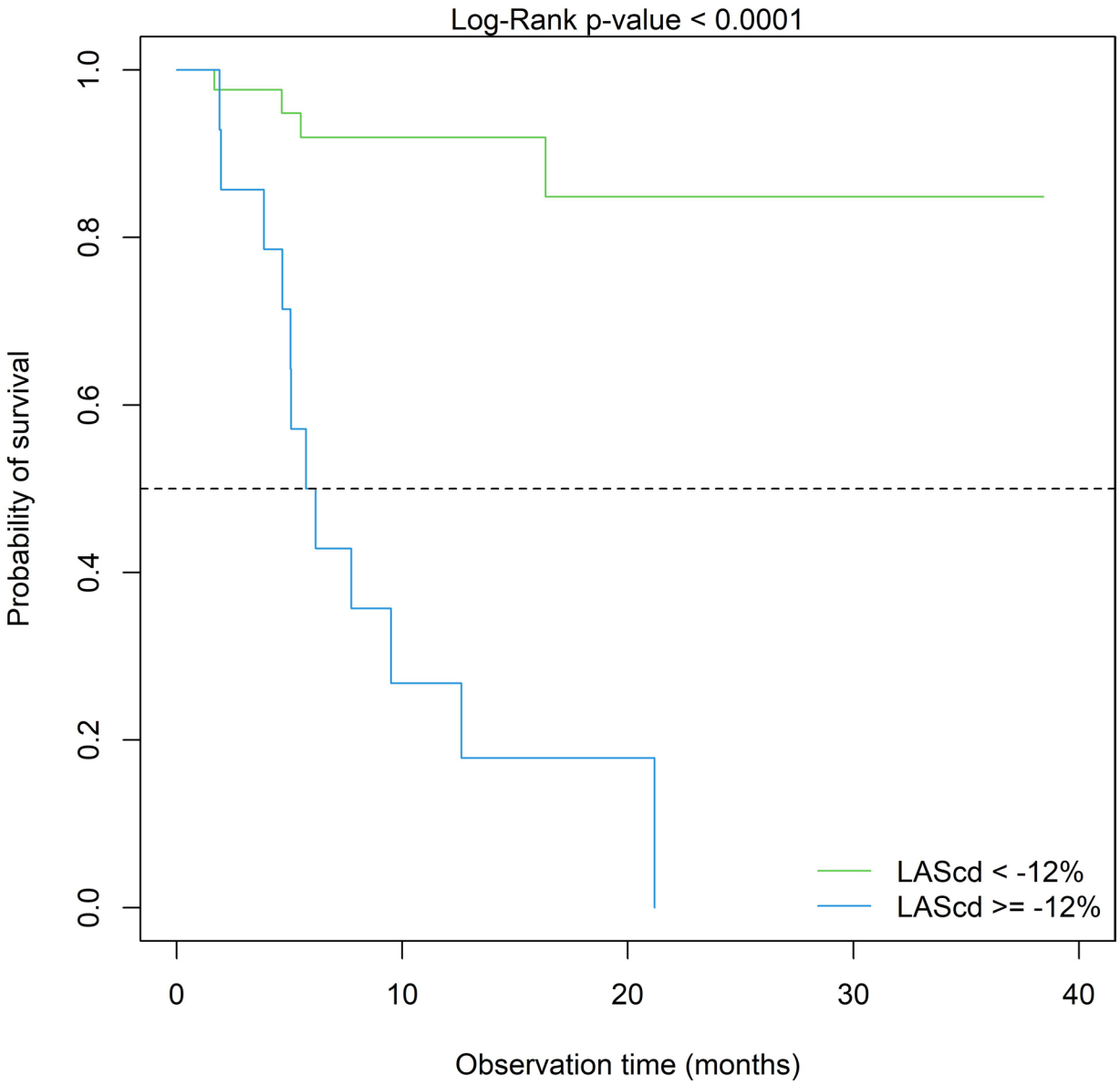

Fig. 2. Kaplan–Meier survival curves in cardiomyopathy patients with different left atrial conduit strain (LAScd).

Both LASr and LAScd had a strong correlation with LASI, and a moderate correlation with some systolic function parameters (LV GLS, LVEF), as well as some diastolic function parameters (average e′ wave velocity, lateral IVRT). There was a moderate correlation between LASr and LASct and NT-proBNP as well as NYHA/or Ross scale score. The detailed correlation analysis is presented in Table 4.

LASI showed a strong correlation with NT-proBNP and NYHA, and a moderate correlation with LVEF. Similarly to LASr and LAScd, LASI correlated with only some of the conventional echocardiographic diastolic dysfunction parameters (Table 4).

When applying the random forest model, the top 3 parameters associated the strongest with adverse outcomes in patients with dilated cardiomyopathy were LASr, LASI and LAScd. The positive predictive value of the model was 66%, negative predictive value 93%, specificity 93%, sensitivity 66%, and ACC 0.88.

Also among patients with DCM and an arrhythmic endpoint, there were significant differences in terms of LASI (0.90 [IQR 0.57; 2.09] vs. 0.23 [IQR 0.16; 0.52] p-value 0.027), LASr (11.03% ± 6.81 vs. 29.10% ± 13.73, p-value 0.017) and LAScd (− 8.08% ± 5.32 vs. − 23.12% ± 12.13, p-value 0.023).

When compared to the control group, patients with DCM without adverse outcomes differed significantly from the control group in terms of: LASI (0.22 [IQR 0.16; 0.42] vs. 0.12 [IQR 0.10; 0.14] p-value < 0.001), LAVi (31.61 ± 12.29 vs. 17.88 ± 5.12 p-value < 0.001), LASr (30.10% [24.20; 41.40] vs. 50.65% [44.90; 56.10] p-value < 0.001), LAScd (− 25.49% ± 10.99% vs. − 38.77% ± 10.34% p-value < 0.001), and LASct (− 6.21% ± 8.91% vs. − 13.77% ± 4.25% p-value < 0.001). The detailed data concerning differences in the echocardiographic parameters between DCM patients without adverse outcomes and the control group are presented in Table S3, Supplementary Materials.

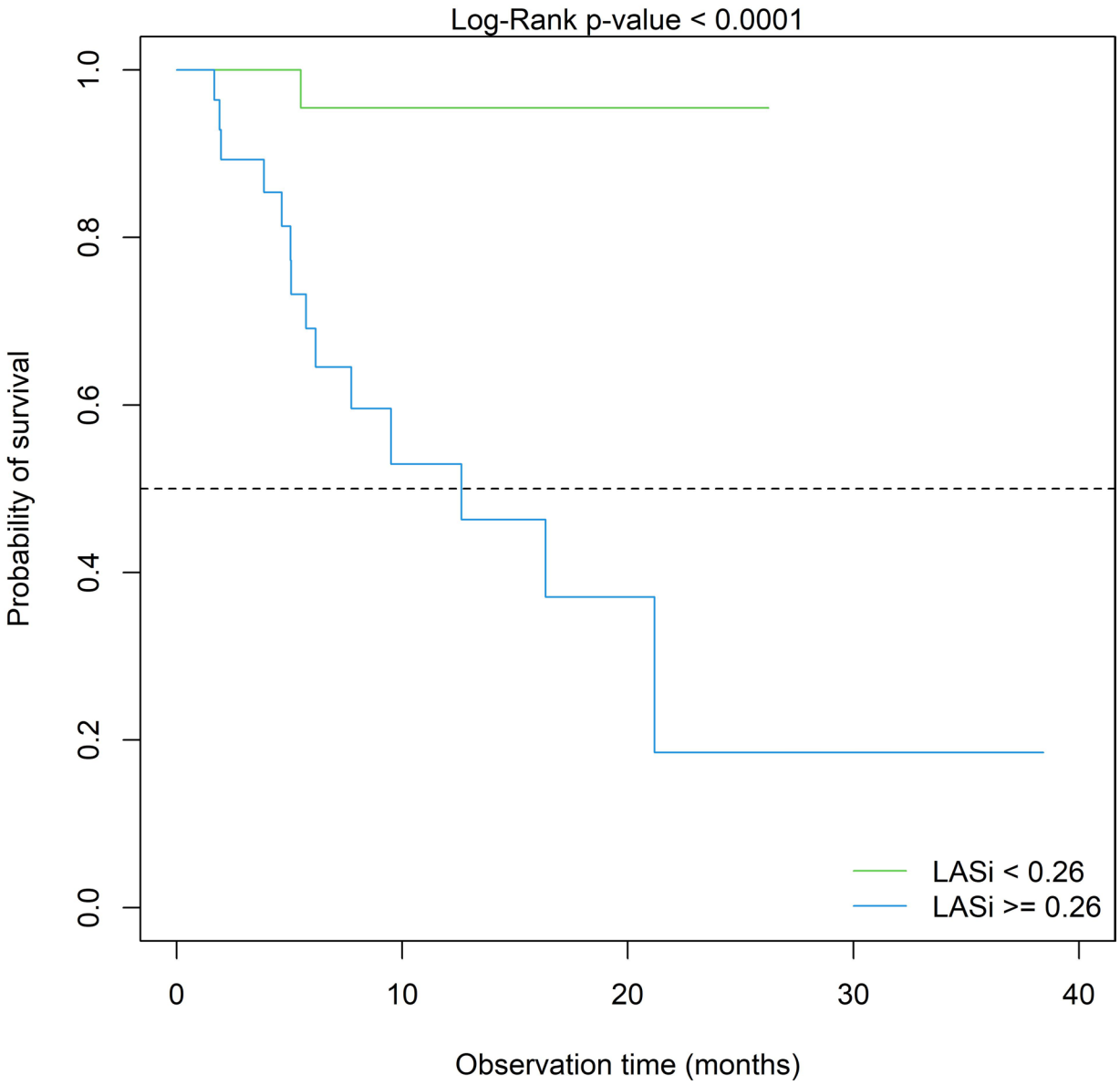

Fig. 3. Kaplan–Meier survival curves in cardiomyopathy patients with different left atrial stiffness index (LASI).

Hypertrophic cardiomyopathy

There were 21 patients with hypertrophic cardiomyopathy, 7 of them (33%) experienced an adverse outcome (all of them had an arrhythmic adverse outcome), and one died due to sudden cardiac death. The differences in HCM children with and without adverse outcomes are presented in Table 5. Patients with adverse outcomes had significantly greater NT-proBNP and troponin levels when compared to patients without adverse outcomes. There were no differences in terms of age or NYHA/Ross scale score.

In terms of echocardiographic parameters there were significant differences in terms of LASI, LAVi, LASr, LAScd, ventricular wall thickness (IVSd and LVPWd *z*-scores), and some diastolic function parameters (IVRT, e′/a′ medial and lateral, average e′ and E/e′) between patients with and without adverse outcomes (Table 5). However, there were no significant differences in terms of LASct, MR, or LVOT gradient. Furthermore, not all diastolic dysfunction parameters were different between the 2 subgroups (Table 5).

Correlation analysis showed a strong correlation between LASr and LASI, LVEF, and lateral a′ (Table 4). There was a moderate correlation between LASr and LAVI, MR, some diastolic function parameters (medial IVRT, medial E/e′), and NT-proBNP. LAScd showed a strong correlation with NT-proBNP and medial e′, and a moderate correlation with NYHA/Ross scale score, troponin, LASI, LAVi, MR, and some diastolic dysfunction parameters. Detailed correlation analysis is presented in Table 4.

On the random forest model, the top 3 parameters most helpful in predicting patients with adverse outcomes included the following LAScd, LASr, and left ventricular ejection fraction with a 100% positive predictive value, 89% negative predictive value, 50% sensitivity, 100% specificity, and ACC 0.90.

	Adverse outcome	No adverse outcome	*p*-value
Age [years]	14 (4–17)	8.0 (1.17; 11.0)	0.093
NYHA/Ross scale	4 (3–4)	1 (1–1)	**< 0.001**
Positive family history	1 (14%)	5 (24%)	0.595
NT-proBNP [pg/ml]	3851.0 (2448; 7033)	49 (30; 323)	**0.001**
Troponin [ng/ml]	25.9 (1.9; 95.4)	1.8 (0.99; 20.6)	0.134
LASI	0.93 (0.69; 3.07)	0.22 (0.16; 0.42)	**0.001**
LAVi [ml/m^2]	49.85 ± 39.03	31.61 ± 12.29	0.084
LASr [%]	10.70 ± 7.01	31.79 ± 12.17	**< 0.001**
LAScd [%]	− 7.43 ± 4.41	− 25.49 ± 10.99	**< 0.001**
LASct [%]	− 3.29 ± 5.06	− 6.21 ± 8.91	0.421
LV GLS [%]	− 5.97 ± 3.00	− 16.69 ± 3.80	**< 0.001**
LVEF [%]	24.10 ± 6.57	42.26 ± 7.68	**< 0.001**
LVIDd *z*-score	5.12 ± 0.89	3.27 ± 1.26	**0.001**
MR grade	1 (1; 2)	1 (0; 2)	0.656
E [cm/s]	73.67 ± 20.64	89.51 ± 18.53	0.068
DT [ms]	124 (74–139)	129.5 (107; 152)	0.361
A [cm/s]	32.03 ± 11.26	57.47 ± 15.61	**0.001**
E/A	2.15 (1.95–2.90)	1.46 (1.31; 1.63)	**0.042**
IVRT med [ms]	70.0 ± 29.81	63.86 ± 18.49	0.521
e′ med [cm/s]	7.15 ± 3.14	9.67 ± 2.56	**0.043**
a′ med. [cm/s]	3.69 (3.48; 7.18)	5.77 (5.44; 6.53)	0.232
e′/a′ med	1.64 ± 0.22	1.71 ± 0.60	0.770
IVRT lat [ms]	96.83 ± 27.89	56.52 ± 17,09	**< 0.001**
e′ lat [cm/s]	8.49 ± 3.75	13.96 ± 4.89	**0.018**
a′ lat [cm/s]	3.67 ± 0.71	6.66 ± 2.80	**0.017**
e′/a′ lat	2.23 (1.61; 2.67)	1.87 (1.79; 2.88)	0.838
e′ avg [cm/s]	8.77 ± 2.17	11.81 ± 3.22	**0.0398**
E/e′ avg	8.15 (7.42; 10.21)	6.85 (5.96; 8.96)	0.210

Table 3. Differences between patients with dilated cardiomyopathy with and without adverse outcomes. Data are presented as mean and ± standard deviation or median and (inter-quartile range) depending on the variables' distribution. *A* peak atrial (A-wave) mitral velocity, *a′* tissue Doppler late mitral annulus velocity, *avg* average, *DT* deceleration time, *E* peak early (E-wave) mitral velocity, *e′* tissue Doppler early mitral annulus velocity, *IVRT* isovolumetric relaxation time, *LAScd* left atrial conduit strain, *LASct* left atrial contraction strain, *LASI* left atrial stiffness index, *LASr* left atrial reservoir strain, *lat* lateral, *LAVi* left atrial volume indexed, *LVEF* left ventricular ejection fraction, *LV GLS* left ventricular global longitudinal strain, *LVIDd* left ventricular internal diastolic dimension, *med* medial, *MR* mitral regurgitation. Significant values are in bold.

Patients with HCM, who did not reach the endpoint in comparison to the control group, had significantly different LASI (0.20 [IQR 0.18; 0.27] vs. 0.12 [IQR 0.10; 0.14], *p*-value < 0.001), LASr (37.40% [32.10; 39.70] vs. 50.65% [44.90; 56.10], *p*-value < 0.001), LAScd (− 23.75% [− 30.20; − 21.20] vs. − 36.90% [− 44.15; − 31.60], *p*-value < 0.001) and LASct (− 10.05% [− 12.50; − 7.70] vs. − 14.25% [− 17.50; − 10.65], *p*-value 0.03). Furthermore, there were significant differences between the 2 subgroups in terms of LV GLS and some diastolic function parameters (e′, e′/a′ medial and lateral, average E/e′, lateral IVRT). The detailed data are presented in Table S4 in the Supplementary Materials.

Interobserver variability was analyzed in terms of left atrial strain parameters using Lin's concordance coefficient. The agreement between the observers was 0.928 (CI 0.774; 0.979) for LASr, 0.948 (CI 0.843; 0.984) for LAScd, and 0.984 (CI 0.947; 0.995) for LASct.

Discussion

Conventional echocardiographic diastolic function parameters outlined in the adult guidelines are characterized by low interobserver agreement in assessing differences between healthy children and pediatric patients with cardiomyopathies[1]. Furthermore, classification of diastolic dysfunction into grades is often difficult due to various parameters measured, their variability in time, dependence on the loading conditions, as well as problems with classification of borderline cases. Therefore, in the pediatric population the search for new, easily obtainable and reproducible parameters is crucial. Left atrial strain, which reflects loading abnormalities that occur secondarily to impaired left ventricular relaxation and compliance, seems to be a promising parameter in pediatric patients with primary myocardial diseases such as cardiomyopathies. It was proven to be superior to E/e′ measurements in predicting elevated pulmonary pressure in children qualified for heart transplant[23]. To our knowledge, there are no studies concerning left atrial strain and survival in children with cardiomyopathies. In our pilot study,

	DCM			HCM		
	LASI	LASr	LAScd	LASI	LASr	LAScd
NYHA/Ross scale	**0.81***	**−0.65***	**0.66***	0.28*	−0.32*	**0.44***
Nt-proBNP	**0.75***	**−0.66***	**0.64***	**0.54***	**−0.48***	**0.72***
Troponin	**0.39***	−0.28*	0.34*	0.35*	−0.44*	**0.61***
LASI	1.00*	**−0.91***	**0.72***	1.00*	**−0.81***	**0.65***
LAVI	0.36*	−0.29*	**0.54***	**0.63***	**−0.57***	**0.66***
LASr	**−0.69***	1.00	**−0.83**	**−0.81***	1.00	**−0.83**
LAScd	**0.51***	**−0.83**	1.00	**0.65***	**−0.83**	1.00
LASct	**0.45***	**−0.48**	−0.09	0.19*	−0.12*	−0.37*
LV GLS	0.41*	**−0.64**	**0.48**	**0.48***	−0.32*	0.33*
LVEF	**−0.53***	**0.59**	**−0.54**	−0.33*	**0.75**	−0.53
MR grade	0.31*	−0.23*	0.19*	**0.628***	**−0.445***	**0.590**
E	−0.04*	0.31	**−0.50**	−0.15*	0.53	**−0.67**
DT	−0.31*	0.22*	−0.33*	−0.11*	−0.15	0.10
A	**−0.47***	**0.47**	−0.34	−0.08*	0.55	**−0.60**
E/A	0.35*	−0.36*	0.26*	0.02*	−0.02	−0.10
IVRT med	0.11*	0.03	−0.03	**0.51***	**−0.53***	**0.55***
e′ med	−0.21*	0.29	−0.26	**−0.75***	0.53	**−0.75**
a′ med	−0.19*	0.36	−0.11	−0.07*	0.05	−0.36
e′/a′ med	0.01*	−0.05*	−0.08*	**−0.65***	0.56	−0.59
E/e′ med	**0.39***	−0.11*	−0.04*	**0.76***	**−0.46***	**0.54***
IVRT lat	**0.42***	**−0.53**	**0.39**	0.14*	−0.29*	0.08*
e′ lat	**−0.55***	**0.58**	**−0.49**	**−0.69***	0.60	−0.58
a′ lat	**−0.61***	**0.50***	−0.34*	0.22*	**0.72**	**−0.61**
e′/a′ lat	−0.20*	0.10*	−0.15*	**−0.72***	0.22	−0.22
E/e′ lat	**0.71***	**−0.42***	0.23*	**0.75***	−0.35*	0.36*
e′ avg	**−0.40***	**0.54**	**−0.43**	0.27*	−0.09	0.16
E/e′ avg	**0.67***	−0.34*	0.12*	0.27*	−0.11*	0.18*

Table 4. Correlation analysis of echocardiographic parameters in the dilated and hypertrophic cardiomyopathy groups. Data are presented as *r* value, correlations with p-value < 0.05 were bolded, *Spearman's correlation. *A* peak atrial (A-wave) mitral velocity, *a′* tissue Doppler late mitral annulus velocity, *avg* average, *DCM* dilated cardiomyopathy, *DT* deceleration time, *E* peak early (E-wave) mitral velocity, *e′* tissue Doppler early mitral annulus velocity, *IVRT* isovolumetric relaxation time, *HCM* hypertrophic cardiomyopathy, *LAScd* left atrial conduit strain, *LASct* left atrial contraction strain, *LASI* left atrial stiffness index, *LASr* left atrial reservoir strain, *lat* lateral, *LAVi* left atrial volume indexed, *LVEF* left ventricular ejection fraction, *LV GLS* left ventricular global longitudinal strain, *med* medial, *MR* mitral regurgitation.

both LASr and LAScd were associated with adverse outcomes in children with cardiomyopathies, whereas there were no significant differences in terms of LASct. Similarly to what has been reported in adults, pediatric patients with LASr < 20% as well as LAScd ≥ − 12% had worse survival on the Kaplan–Meier curves[2,4]. Furthermore, on the random forest model both parameters were among the top 3 parameters most helpful in predicting adverse outcomes, but one must keep in mind the models' moderate sensitivity and excellent specificity. Thus, both left atrial reservoir and conduit strain appear to be noteworthy parameters in the risk assessment of pediatric cardiomyopathy patients.

Left atrial stiffness index, which is the ratio of left atrial reservoir strain to a conventional echocardiographic diastolic parameter (E/e′), has recently received attention in the adult population[24–27]. In patients with heart failure with preserved ejection fraction (HFpEF), increased left atrial stiffness index (> 0.26) has been associated with substantial risk of death or heart failure hospitalizations and was superior to conventional echocardiographic measurements of elevated left ventricular filling pressures[24]. It predicted elevated NT-proBNP and was associated with reduced exercise tolerance in adults with HFpEF[26,27]. In adults with HCM and DCM it was suggested that LASI might be superior to left atrial strain alone in terms of predicting elevated pulmonary artery pressures and thus be more accurate in detecting ventricular diastolic dysfunction[25]. We did not find any studies on LASI in pediatric cardiomyopathies. In our analysis LASI was significantly greater in patients with adverse outcomes, and, similarly to adults, LASI ≥ 0.26 was associated with significantly reduced survival[24]. Furthermore, LASI was among the top 3 echocardiographic variables helpful in predicting adverse outcomes in pediatric cardiomyopathy patients. LASI was also significantly greater among patients with cardiomyopathies without adverse outcomes compared to control subjects, which shows its potential in assessing early diastolic dysfunction. Therefore, LASI shines as an easily obtainable parameter that might be helpful in assessing risk stratification among cardiomyopathy patients as well as differentiating patients with myocardial diseases from healthy individuals.

	Adverse outcome	No adverse outcome	*p*-value
Age [years]	13.0 (8–17)	6.5 (0.5; 15)	0.12
NYHA/Ross scale	2 (1–2)	1 (1; 2)	0.054
Positive family history	5 (71%)	6 (43%)	0.216
Nt-proBNP [pg/ml]	3415.0 (1463.0; 6388.0)	133.0 (42.0; 748.0)	**0.003**
Troponin [ng/ml]	59.20 (18.8; 215)	5.1 (1.5; 10.4)	**0.007**
LASI	0.72 ± 0.44	0.22 ± 0.11	**< 0.001**
LAVi [ml/m^2]	47.07 ± 15.97	21.07 ± 6.56	**< 0.001**
LASr [%]	20.87 ± 6.58	36.66 ± 5.53	**< 0.001**
LAScd [%]	− 11.66 ± 6.01	− 25.44 ± 7.64	**< 0.001**
LASct [%]	− 10.10 (− 11; − 4.5)	− 10.5 (− 12.5; − 7.7)	0.74
LV GLS [%]	− 16.02 (− 20.7; − 3.73)	− 18.53 (− 19.83; − 13.87)	0.74
LVEF [%]	55.29 ± 12.66	62.50 ± 4.91	0.072
LVIDd z-score	− 1.95 ± 2.83	− 1.61 ± 2.09	0.76
IVSd z-score	5.99 (5.54; 21.11)	3.93 (2.43; 6.08)	**0.023**
LVPWd z-score	6.17 ± 3.97	2.44 ± 1.79	**0.007**
MR grade	1 (1; 1)	0 (0; 1)	0.24
E [cm/s]	82.07 ± 38.08	87.61 ± 21.69	0.67
DT [ms]	132.86 ± 65.72	127.29 ± 41.71	0.81
A [cm/s]	51.58 ± 26.09	61.59 ± 18.75	0.35
E/A	1.53 (1.52; 1.64)	1.47 (1.29; 1.57)	0.31
IVRT med [ms]	149.17 ± 82.06	72.92 ± 26.41	**0.006**
e′ med [cm/s]	5.33 ± 1.86	9.24 ± 2.85	**0.004**
a′ med [cm/s]	6.70 ± 2.49	6.58 ± 1.61	0.91
e′/a′ med	0.80 ± 0.41	1.46 ± 0.51	**0.033**
IVRT lat [ms]	130.86 ± 64.12	79.36 ± 27.28	**0.030**
e′ lat [cm/s]	8.08 ± 4.18	11.92 ± 2.86	**0.025**
a′ lat [cm/s]	9.27 ± 2.98	7.68 ± 1.25	0.11
e′/a′ lat	0.87 ± 0.44	1.62 ± 0.59	**0.014**
e′ avg [cm/s]	6.71 ± 2.83	10.58 ± 2.68	**0.007**
E/e′ avg	13.07 ± 5.42	8.37 ± 2.53	**0.015**
LVOT max [mmHg]	17.0 (7.0; 51.0)	7.5 (5.0; 11.0)	0.17

Table 5. Differences between patients with hypertrophic cardiomyopathy with and without adverse outcomes. Data are presented as mean and ± standard deviation or median and (inter-quartile range) depending on the distribution of the variables. *A* peak atrial (A-wave) mitral velocity, *a′* tissue Doppler late mitral annulus velocity, *avg* average, *DT* deceleration time, *E* peak early (E-wave) mitral velocity, *e′* tissue Doppler early mitral annulus velocity, *IVRT* isovolumetric relaxation time, *IVSd* interventricular septum dimension, *LAScd* left atrial conduit strain, *LASct* left atrial contraction strain, *LASI* left atrial stiffness index, *LASr* left atrial reservoir strain, *lat* lateral, *LAVi* left atrial volume indexed, *LVEF* left ventricular ejection fraction, *LV GLS* left ventricular global longitudinal strain, *LVIDd* left ventricular, *LVOT max* maximal left ventricular outflow tract pressure gradient, *LVPWd* left ventricular posterior wall dimension, internal diastolic dimension, *med* medial, *MR* mitral regurgitation. Significant values are in bold.

Dilated cardiomyopathy

In our study patients with dilated cardiomyopathy and adverse outcomes had significantly lower LASr and less negative LAScd. To our knowledge, no previous studies concerning left atrial strain and survival in pediatric DCM have been published. Furthermore, adult studies concerning left atrial function in dilated cardiomyopathy are mostly based on CMR rather than echocardiography[2,28]. Raafs et al. showed that LAScd < 12% was a predictor of freedom of adverse events or rehospitalization due to heart failure in adults and was superior in predicting adverse outcomes to LV GLS, LVEF, as well as LAVi[2]. In another adult CMR study on patients with heart failure, left atrial reservoir strain was associated with adverse cardiovascular events independently of late gadolinium enhancement[28]. Our results are in line with previous adult studies, because both LASr and LAScd were associated with adverse outcomes[2,29]. Furthermore, they were both, together with LASI, among the top parameters helpful in predicting adverse outcomes among children with DCM, although one has to keep in mind the model's moderate sensitivity and high specificity. In our study, not all diastolic dysfunction parameters differed between patients with and without adverse outcomes. For instance, there were no differences in terms of DT, E-wave velocity, E/e′, medial IVRT, or medial a′ wave velocity between DCM children with and without adverse outcomes. This seems to agree with previous studies, in which the usefulness of conventional diastolic dysfunction parameters in the pediatric cardiomyopathy population has been questioned[1]. Furthermore, in the random forest model,

these parameters were inferior to LASr and LAScd. Thus, conventional echocardiographic diastolic dysfunction parameters seem to be imperfect in outlining patients with and without adverse outcomes.

When compared to the control group, patients with DCM without adverse outcomes differed in terms of all 3 measured left atrial strain parameters, LASI, and only some of the conventional echocardiographic diastolic function parameters. Similarly to Sabatino et al., we observed greater E/e′ ratio and LAVi as well as lower left atrial peak systolic strain[10]. We also did not observe significant differences in terms of DT or E/A ratio, which again points to the imperfection of the conventional diastolic dysfunction parameters in the pediatric population[10]. Because all left atrial strain parameters and LASI were different between the control group and DCM patients without adverse outcomes, it points toward their value not only in assessing pediatric diastolic dysfunction but also in discriminating healthy control subjects from early stages of dilated cardiomyopathy.

In adults, A-wave velocity, E/A wave ratio and LV GLS have been associated with malignant ventricular arrhythmias[30]. Similarly, in our study they were also significantly different between DCM children with and without ventricular arrhythmias. Thus, in our study, we also observed differences in terms of greater LASI, lower LASr, and less negative LAScd, which could be new, additional parameters helpful in predicting arrhythmic events in the pediatric DCM population.

In our study, similarly as reported by Pahl et al., positive family history in children with dilated cardiomyopathy was not associated with adverse outcomes[31]. The role of genetic testing should be stressed because it has been shown that pathogenic or likely pathogenic variants occur independently of family history among pediatric dilated cardiomyopathy patients[32].

Hypertrophic cardiomyopathy

Left atrial strain parameters have been better studied in the HCM adult population; unfavorable outcomes such as heart failure, stroke, or death have been associated with LASr ≤ 23.8% and LAScd ≤ 10.2% on echocardiography[3]. In children, no such values have been defined so far. In our study, LASr and LAScd were significantly different between HCM patients with and without adverse outcomes, which suggests that the abnormalities in the left atrial function and pressures increase with the disease's progression.

In an adult CMR study, it has been shown that impaired LASct appears with the disease's progression and is associated with fibrosis, whereas lower LAScd is abnormal in earlier stages of the disease[33]. This observation might not be valid in the pediatric population. In our study, patients with HCM and adverse outcomes did not differ significantly from HCM patients without end-point in terms of LASct, however, they had significantly different LASr and LAScd. Thus, abnormalities associated with the most severe disease progression in the pediatric population might not be identical to the adult population. However, further studies regarding survival in pediatric HCM are necessary to assess this finding.

LASr and LAScd were significantly different between the control group and HCM patients without adverse outcomes, whereas the difference in terms of LASct was borderline significant (p-value 0.03). In the study by Jhaveri et al. on children and young adults (up to 25 years old) with HCM, both LASr and LASct were reduced in phenotype-positive patients compared to genotype-positive[11]. Phenotype-positive patients and the control group differed in terms of LASr in the 2-chamber view; however, no difference was found in terms of LASct[11]. Thus, both LASr and LAScd seem to be valuable parameters in differentiating healthy individuals from early stages of pediatric hypertrophic cardiomyopathy. The usefulness of LASct in the pediatric population is yet to be determined.

Alis et al. showed that abnormalities in LASr and LAScd on CMR preceded enlargement of the left atrial volumes in children with HCM[12]. This is in agreement with our results, although we did not observe differences in terms of LAVi on echocardiography between control patients and HCM patients without the end-point of the study; thus, we observed significant differences in terms of LASr and LAScd. It appears, that LASr and LAScd both on CMR and echocardiography are more accurate in depicting left atrial abnormalities than LAVi. For this reason, left atrial strain parameters may be more useful in differentiating healthy controls from early stages of pediatric hypertrophic cardiomyopathy.

In children with HCM, it has been suggested that left ventricular outflow tract obstruction leads to abnormalities in left atrial volume, left atrial total strain and conduit strain[34]. However, we believe that abnormalities in the left atrial strain are caused not only by the degree of the left ventricular outflow tract obstruction, but also reflect changes in the diastolic dysfunction and increased stiffness of the ventricle itself. On the contrary, in our study HCM patients with and without adverse outcome did not differ significantly in terms of left ventricular outflow tract obstruction; thus, they differed in terms of LASI, left atrial reservoir and conduit strain.

The relationship between family history and sudden cardiac death in the pediatric hypertrophic cardiomyopathy population is disputable. So far, family history has not been included in the HCM-Risk KIDS scale as a risk factor[35]. Similarly to this finding, in our study positive family history was not associated with increased risk of adverse outcomes.

In adults left atrial volume index (LAVi), left ventricular global longitudinal strain, as well as mechanical dispersion were associated with an adequate ICD therapy, and therefore the occurrence of malignant ventricular arrhythmia[36]. To our knowledge, no studies concerning the association between ventricular arrhythmia and atrial strain echocardiography in children with hypertrophic cardiomyopathy have been published. In our study, in HCM patients with adverse events (who all had arrhythmic adverse events) LAVi was significantly greater than in those without; thus, they did not differ significantly in terms of LV GLS. This suggests that LV GLS abnormalities might progress with age, and pediatric risk factors for adverse outcomes are not identical to the adult ones.

Left ventricular non-compaction

There is scarce literature concerning left atrial strain in left ventricular non-compaction cardiomyopathy. In adults, reduced LASr was a predictor of exacerbation of heart failure[5]. Furthermore, LASr and LASct were different between patients with multiple gene variants with LVNC and genotype-negative patients, which suggests a more severe disease in patients with multiple mutations[6]. In our study, due to a limited number of patients, we could not perform analysis in the LVNC group only. As left ventricular-non compaction is a heterogenous disorder, left atrial strain might be an easily obtainable parameter helpful in outlining those with cardiovascular risk. Thus, the role of genetic testing in left ventricular non-compaction should not be understated, because various cardiomyopathy phenotypes, including hypertrabeculation, may be present among different family members[37].

Some limitations to the study should be outlined. Because cardiomyopathies in children are rare diseases and this was a single-center study, the sample size was relatively small. For this reason, multicenter studies on a larger number of patients are crucial to more accurately assess left atrial strain values that would be helpful to identify patients with the greatest cardiovascular risk. Furthermore, due to the limited sample size, we did not assess the grade of the diastolic dysfunction abnormalities. Another limitation is that we only used Phillips software for left atrial strain assessment; therefore, variability of left atrial strain in the pediatric population using different software was not assessed. The observation time of the study was relatively short; thus, while this was a pilot study, we believe it sheds light on new and promising echocardiographic parameters helpful in outlining patients with pediatric cardiomyopathies at greatest cardiovascular risk.

Conclusions

Left atrial reservoir and conduit strain as well as left atrial stiffness index appear to be promising new parameters in predicting adverse outcomes in pediatric patients with cardiomyopathies. Moreover, they appear to help differentiate healthy individuals from those with the early stages of dilated and hypertrophic cardiomyopathies.

Data availability

The datasets analyzed during the current study are available from the corresponding author on reasonable request.

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Author contributions

KLW, BW conceived the experiment; KLW, CN, KO conducted the experiment; KLW analyzed the results and wrote the original manuscript. BW supervised the work on the manuscript. All authors reviewed the manuscript.

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Competing interests

The authors declare no competing interests.

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7. PODSUMOWANIE

W opublikowanych pracach przedstawiono nowe parametry elektrokardiograficzne i echokardiograficzne pomocne w identyfikacji dzieci z niekorzystnym przebiegiem kardiomiopatii rozstrzeniowej, przerostowej i niescaleniem mięśnia lewej komory. Jednocześnie, wyróżniono parametry mające znaczenie w wyodrębnianiu pacjentów z łagodnym fenotypem od populacji zdrowych dzieci. Przeanalizowano również wyniki opublikowanych badań dotyczących niescalenia mięśnia lewej komory u pacjentów pediatrycznych.

Pierwsza praca jest przeglądem systematycznym artykułów dotyczących niescalenia mięśnia lewej komory (LVNC) w populacji dziecięcej. W tym temacie opublikowano liczne opisy przypadków, ale niewiele jest badań na większych grupach pacjentów. Brakowało przeglądu systematycznego porządkującego dotychczasowe doniesienia dotyczące populacji pediatrycznej. Stosując protokół PRISMA (*Preferred Reporting Items for Systematic Reviews and Meta-Analyses*) w bazach medycznych Pubmed, Cochrane oraz Embase wyszukano artykuły związane z dziecięcym LVNC oraz niekorzystnym przebiegiem choroby (definiowanym jako: częstoskurcz komorowy, zakrzepica, udar, niewydolność serca, kwalifikacja do- lub przeszczep serca, zgon). Zidentyfikowano 1983 artykuły, z których ostatecznie 23 spełniały kryteria włączenia do analizy. W przeglądzie systematycznym pokazano, że niektóre parametry elektrokardiograficzne (zaburzenia repolaryzacji pod postacią nieprawidłowości załamka T, większa wartość kąta QRS-T) oraz echokardiograficzne (obniżona frakcja wyrzutowa lewej komory (LVEF), powiększona lewa komora (LVEDd *z*-score), większy stosunek części niescalonej do scalonej wsierdzia czy obniżone wartości odkształcenia lewej komory (LV GLS)) są związane z niekorzystnym przebiegiem choroby. W publikacji omówiono wartość diagnostyczną rezonansu magnetycznego serca u pacjentów pediatrycznych z LVNC. Obecność późnego wzmocnienia kontrastowego w badaniu rezonansu magnetycznego ma znaczenie rokownicze u nastolatków, natomiast nie została powiązana z niekorzystnym przebiegiem choroby u młodszych dzieci co może być związane z pojawianiem się włóknienia w późniejszym wieku. W przeglądzie systematycznym przeanalizowano również związek LVNC z arytmią, wrodzonymi wadami serca, współwystępowaniem innego typu kardiomiopatii oraz z genotypem. Dzięki obszernej analizie literatury wyodrębniono różnorodne czynniki pomocne w odróżnianiu pacjentów z łagodnym fenotypem od wymagających większej uwagi klinicznej. W publikacji uporządkowano doniesienia dotyczące niescalenia mięśnia lewej komory u dzieci, omówiono różnorodne stosowane kryteria diagnostyczne i wyróżniono czynniki związane z niekorzystnym przebiegiem choroby w tej heterogennej grupie.

W drugiej pracy przeanalizowano zapisy elektrokardiograficzne oraz stężenie biomarkerów sercowych w surowicy u dzieci z kardiomiopatią. Uwzględniono 42 pacjentów w grupie badanej (19 z kardiomiopatią rozstrzeniową, 17 z przerostową oraz 6 z niescaleniem mięśnia lewej komory) oraz 19 w grupie kontrolnej. U 13 pacjentów z kardiomiopatią stwierdzono niekorzystny punkt końcowy w czasie 13 miesięcy obserwacji. Wykazano, że u dzieci z kardiomiopatią z niekorzystnym przebiegiem choroby kąt QRS-T>120º w zapisie EKG oraz nieprawidłowe stężenie troponiny I i NT-proBNP w surowicy krwi są związane z gorszą przeżywalnością. Wartość kąta QRS-T była istotnie wyższa u pacjentów z punktem końcowym niż u dzieci bez punktu końcowego (133,2º±23º vs. 64,7º±28º, p<0,001); analogicznie w podgrupach DCM i HCM również zaobserwowano taką różnicę (odpowiednio 133,7º±22,8º vs. 48,2º±22,9º p<0,001 i 132,5º±26º vs. 84,6º± 25,69º p=0,004). Co ciekawe, wartość kąta QRS-T była istotnie większa niezależnie od tego czy punkt końcowy był związany z arytmią (137,2º±25,3º vs. 70,1º±31,8º p<0,001) czy nasileniem niewydolności serca (133,7º±22,8º vs. 74,7º±36,6º p<0,001). W celu oceny wartości kąta QRS-T w przewidywaniu punktu końcowego przeprowadzono analizę używając modelu klasyfikacji lasu losowego, który wykazał wyższość tego parametru nad innymi tradycyjnie ocenianymi parametrami w zapisie EKG takimi jak: odcinek PQ, zespół QRS, QTc, zmiany odcinka ST czy nieprawidłowości załamka T. Obecność zmian w zapisie EKG u pacjentów z kardiomiopatią jest dość powszechna, jednak są to najczęściej zmiany niespecyficzne. Dotychczas brakowało precyzyjnego parametru, który pozwoliłby ilościowo zmierzyć nieprawidłowości i wyróżnić pacjentów z największym ryzykiem niekorzystnego przebiegu choroby. Jednak, interpretując wyniki badań należy mieć na uwadze stosunkowo niewielką grupę badaną i traktować je jako badania pilotażowe.

W drugiej pracy przeanalizowano również różnice pomiędzy zapisami EKG dzieci z kardiomiopatią oraz zapisami zdrowych dzieci. Wartość kąta QRS-T była istotnie większa u pacjentów z DCM, HCM i LVNC niż w grupie kontrolnej (odpowiednio: 75º vs. 41º, p=0,007; 100º vs. 41º, p<0,001; 64º vs. 41º, p=0,03). Wartość tego parametru różniła się istotnie pomiędzy zapisami dzieci z łagodnym fenotypem HCM a zapisami zdrowych dzieci (84,6º ± 25,69º vs. 40,6º ± 23,22º p<0,001), nie zaobserwowano jednak takiej różnicy porównując wyniki podgrupy DCM z łagodnym fenotypem z wynikami grupy kontrolnej (48,2º± 22,9º vs. 40,6º± 23,22º p=0,37). W związku z tym ocena wartości kąta QRS-T może służyć do odróżniania pacjentów z kardiomiopatią od zdrowych dzieci, a w szczególności dzieci z wczesnym stadium kardiomiopatii przerostowej. Wyniki te są istotne w związku z powszechną dostępnością do 12-odprowadzeniowego badania EKG. Warto jednak zaznaczyć, że obserwacje te wymagają przeprowadzenia badań na większej grupie chorych.

W trzeciej pracy przedstawiono analizę badań echokardiograficznych wykonanych u dzieci z kardiomiopatią oraz w grupie kontrolnej. W badaniu uwzględniono 56 pacjentów; 28 z DCM, 21 z HCM, 7 z LVNC oraz 28 w grupie kontrolnej. Nie było istotnych różnic w zakresie wieku, płci i BMI pomiędzy pacjentami z kardiomiopatią a pacjentami w grupie kontrolnej. W czasie obserwacji u 16 pacjentów (29%) z kardiomiopatią zaobserwowano niekorzystny punkt końcowy. Badania echokardiograficzne przeanalizowano oceniając: tradycyjne parametry funkcji rozkurczowej lewej komory, odkształcenie lewego przedsionka (*strain*) metodą śledzenia markerów akustycznych (*Speckle Tracking Echocardiography* STE) w fazie rezerwuarowej - *left atrial strain during reservoir phase* (LASr), w fazie jego skurczu - *left atrial strain during contraction phase* (LASct), w fazie konduitowej - *left atrial strain during conduit phase* (LAScd) oraz sztywność lewego przedsionka (*Left Atrial Stiffness Index* LASI) czyli stosunek (E/e')/LASr. Ocena odkształcenia lewego przedsionka nie była dotychczas przebadana u pacjentów pediatrycznych z kardiomiopatią pod kątem znaczenia rokowniczego [25]. W badaniu wykazano istotne różnice w zakresie wartości LASr, LAScd oraz LASI u dzieci z niekorzystnym punktem końcowym w stosunku do dzieci z łagodnym fenotypem (odpowiednio 16,68% ±8,64% vs. 33,97% ±9,99%, p<0,001; -10,37% ±5,83% vs.-25,50% ±9,24%, p<0,001; 0,69 (IQR 0,34;1,11) vs. 0,21 (IQR 0,16;0,31), p<0,001). Na krzywych przeżywalności Kaplana-Meiera wykazano, że LASr <20%, LAScd ≥ -12% i LASI ≥0,26 są związane z większą śmiertelnością w populacji dzieci z kardiomiopatią. Wyniki te pokazują wartość diagnostyczną oceny odkształcenia lewego przedsionka w kontekście stratyfikacji ryzyka pacjentów pediatrycznych z kardiomiopatią.

W celu zidentyfikowania czynników echokardiograficznych najsilniej związanych z przewidywaniem niekorzystnego przebiegu choroby w badaniu zastosowano model klasyfikacji lasu losowego. Wykazano w nim wyższość LASr i LAScd w stosunku do tradycyjnych parametrów pomiaru funkcji rozkurczowej zarówno u wszystkich pacjentów z kardiomiopatią jak i w podgrupach DCM oraz HCM. Wydaje się być to interesujący punkt wyjściowy, do badań na większych grupach pacjentów, jako iż konwencjonalne parametry funkcji rozkurczowej są niedoskonałe w populacji pediatrycznej w związku ze zmiennością z wiekiem oraz niską zgodnością pomiarów [23].

W trzeciej publikacji wykazano też statystycznie istotne różnice w zakresie LASr, LAScd, LASct i LASI pomiędzy pacjentami z HCM i DCM bez punktu końcowego a dziećmi w grupie kontrolnej (odpowiednio w grupie HCM: LASr 37,40% (IQR 32,10;39,70) vs. 50,65% (IQR 44,90;56,10) p<0,001, LAScd -23,75% (IQR -30,20;-21,20) vs. -36,9% (IQR -44,15; -31,60) p<0,001, LASct -10,05% (IQR -12,50;-7,70) vs. -14,25% (IQR -17,50;-10,65) p=0,03, LASI 0,2 (IQR 0,18;0,27) vs. 0,12 (IQR 0,10;0,14) p<0,001); w grupie DCM: : LASr 30,10%

(IQR 24,20; 41,40) vs. 50,65% (IQR 44,90; 56,10) p<0,001, LAScd -25,49% ± 10,99% vs. -38,77% ± 10,34% p<0,001, LASct -6,21% ± 8,91% vs. -13,77% ± 4,25% p<0,001, LASI 0,22 (IQR 0,16;0,42) vs. 0,12 (IQR 0,10;0,14) p<0,001). Parametry te mogą być pomocne we wczesnym rozpoznawania choroby, w szczególności u pacjentów z dodatnim genotypem, i mogą służyć do różnicowania od zdrowej populacji.

Podsumowując, przeprowadzone badania pozwoliły na wyodrębnienie czynników pomocnych w zidentyfikowaniu pacjentów z kardiomiopatią wymagających największej uwagi klinicznej. W oparciu o przeprowadzone badania wykazano różnice w zakresie parametrów elektrokardiograficznych i echokardiograficznych pomiędzy pacjentami z łagodnym fenotypem kardiomiopatii a wynikami badań zdrowych dzieci. Wyniki przeprowadzonych badań są obiecujące, jednak należy mieć na uwadze stosunkowo małą grupę badaną wynikającą z częstości występowania choroby i traktować je jako pilotażowe.

8. WNIOSKI

1. Wartość kąta QRS-T>120º w 12-odprowadzeniowym zapisie pozwala na wyodrębnienie wśród dzieci kardiomiopatią pacjentów z największymi zaburzeniami elektrycznymi mięśnia sercowego i gorszą przeżywalnością
2. Obniżenie odkształcenia lewego przedsionka w fazie rezerwuarowej i konduitowej w badaniu echokardiograficznym metodą śledzenia markerów akustycznych oraz zwiększona sztywność lewego przedsionka są parametrami niekorzystnego rokowania u dzieci z kardiomiopatią.
3. Ocena odkształcenia lewego przedsionka w fazie rezerwuarowej, konduitowej i skurczowej oraz sztywności lewego przedsionka w badaniu echokardiograficznym pozwala na różnicowanie pacjentów z kardiomiopatią z łagodnym fenotypem od zdrowych dzieci.
4. Nieprawidłowe wyniki stężenia biomarkerów sercowych (troponina I, NT-proBNP) są związane z gorszym przeżyciem u pacjentów pediatrycznych z trzema najczęstszymi typami kardiomiopatii.
5. Niescalenie mięśnia lewej komory to heterogenna grupa w populacji pediatrycznej, jednak można wyróżnić podtypy choroby związane z jej niekorzystnym przebiegiem. Badanie EKG, echokardiograficzne, rezonansu magnetycznego oraz genetyczne są pomocne w wyodrębnianiu pacjentów wymagających największej uwagi klinicznej.

9. OPINIA KOMISJI BIOETYCZNEJ

Komisja Bioetyczna
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KB/23/2020

Komisja Bioetyczna przy Warszawskim Uniwersytecie Medycznym
w dniu 03 lutego 2020 r. po zapoznaniu się z wnioskiem:

Lek Katarzyna Łuczak-Woźniak,
Klinika Kardiologii Wieku Dziecięcego
i Pediatrii Ogólnej
ul. Żwirki i Wigury 63A, 02-091 Warszawa

dotyczącym: wyrażenia opinii w sprawie rejestru pt.: „ Ocena stężenia biomarkerów, parametrów elektrokardiograficznych i wyników sercowo-płucnych testu wysiłkowego u dzieci z kardiomiopatią."

wyraża następującą
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- stwierdza, że jest ono dopuszczalne i zgodne z zasadami naukowo-etycznymi*.
- ~~stwierdza, że jest ono niedopuszczalne i niezgodne z zasadami naukowo-etycznymi.*~~

Uwagi Komisji – *verte*

Komisja działa na podstawie art.29 ustawy z dnia 5.12.1996r. o zawodzie lekarza /Dz.U.nr 28/97 poz.152 wraz z późn.zm./, zarządzenia MZiOS z dn.11.05.1999r. w sprawie szczegółowych zasad powoływania i finansowania oraz trybu działania komisji bioetycznych /Dz.U.nr 47 poz.480/, Ustawy prawo farmaceutyczne z dnia 6 września 2001r. (Dz.U.Nr 126, poz. 1381 z późn. zm.) oraz Zarządzenie nr 56/2007 z dnia 15 października 2007r. w sprawie działania Komisji Bioetycznej przy Warszawskim Uniwersytecie Medycznym /Regulamin Komisji Bioetycznej przy Warszawskim Uniwersytecie Medycznym/.
Komisja działa zgodnie z zasadami GCP .

Przewodnicząca Komisji Bioetycznej

Prof. dr hab. n. med. Magdalena Kuźma-Kozakiewicz

*niepotrzebne skreślić

10. OŚWIADCZENIA WSZYSTKICH WSPÓŁAUTORÓW

Warszawa, 19.11.2024
(miejscowość, data)

Prof. dr hab. n. med. Bożena Werner
(imię i nazwisko)

OŚWIADCZENIE

Jako współautor pracy pt. „Left Ventricular Noncompaction-A Systematic Review of Risk Factors in the Pediatric Population" oświadczam, iż mój własny wkład merytoryczny w przygotowanie, przeprowadzenie i opracowanie badań oraz przedstawienie pracy w formie publikacji stanowi:
wkład w przygotowanie koncepcji i metodyki projektu, analizę jego wyników oraz nadzór nad przygotowaniem manuskryptu

Mój udział procentowy w przygotowaniu publikacji określam jako…40.. %.
Wkład Katarzyny Łuczak -Woźniak w powstawanie publikacji określam jako 60 %,
(imię i nazwisko kandydata do stopnia)
obejmował on: przygotowanie projektu i metodyki badania, przeprowadzenie badań, napisanie manuskryptu
(merytoryczny opis wkładu kandydata do stopnia w powstanie publikacji)*

Jednocześnie wyrażam zgodę na wykorzystanie w/w pracy jako część rozprawy doktorskiej lek Katarzyny Łuczak-Woźniak
(imię i nazwisko kandydata do stopnia)

.....
(podpis oświadczającego)

*w szczególności udziału w przygotowaniu koncepcji, metodyki, wykonaniu badań, interpretacji wyników

Warszawa, 19.11.2024
(miejscowość, data)

Prof. dr hab. n. med. Bożena Werner
(imię i nazwisko)

OŚWIADCZENIE

Jako współautor pracy pt. „Electrocardiographic Parameters Associated with Adverse Outcomes in Children with Cardiomyopathies" oświadczam, iż mój własny wkład merytoryczny w przygotowanie, przeprowadzenie i opracowanie badań oraz przedstawienie pracy w formie publikacji stanowi:
wkład w przygotowanie koncepcji i metodyki projektu, merytoryczny nadzór nad prowadzeniem projektu, analizą jego wyników oraz przygotowaniem manuskryptu

Mój udział procentowy w przygotowaniu publikacji określam jako…25.. %.
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obejmował on: przygotowanie projektu i metodyki badania, rekrutację pacjentów, wykonywanie i interpretację badań echokardiograficznych, napisanie manuskryptu
(merytoryczny opis wkładu kandydata do stopnia w powstanie publikacji)*

Jednocześnie wyrażam zgodę na wykorzystanie w/w pracy jako część rozprawy doktorskiej lek Katarzyny Łuczak-Woźniak
(imię i nazwisko kandydata do stopnia)

.....
(podpis oświadczającego)

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Warszawa, 19.11.2024
(miejscowość, data)

Prof. dr hab. n. med. Bożena Werner
(imię i nazwisko)

OŚWIADCZENIE

Jako współautor pracy pt. „Abnormal left atrial strain and left atrial stiffness index are associated with adverse outcomes in children with cardiomyopathies: a pilot study." oświadczam, iż mój własny wkład merytoryczny w przygotowanie, przeprowadzenie i opracowanie badań oraz przedstawienie pracy w formie publikacji stanowi:
wkład w przygotowanie koncepcji i metodyki projektu, merytoryczny nadzór nad prowadzeniem projektu, analizą jego wyników oraz przygotowaniem manuskryptu

Mój udział procentowy w przygotowaniu publikacji określam jako…25.. %.
Wkład Katarzyny Łuczak -Woźniak w powstawanie publikacji określam jako 60 %,
(imię i nazwisko kandydata do stopnia)
obejmował on: przygotowanie projektu i metodyki badania, rekrutację pacjentów, wykonywanie i interpretację badań echokardiograficznych, napisanie manuskryptu
(merytoryczny opis wkładu kandydata do stopnia w powstanie publikacji)*

Jednocześnie wyrażam zgodę na wykorzystanie w/w pracy jako część rozprawy doktorskiej lek Katarzyny Łuczak-Woźniak
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.....
(podpis oświadczającego)

*w szczególności udziału w przygotowaniu koncepcji, metodyki, wykonaniu badań, interpretacji wyników

Warszawa, 19.11.2024
(miejscowość, data)

lek. Klaudia Obsznajczyk
(imię i nazwisko)

OŚWIADCZENIE

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