Uniwersytet Jagielloński

Collegium Medicum

Lidia Stopyra

Przebieg zakażenia SARS-CoV-2 i powikłań zakażenia u dzieci

The course of SARS-CoV-2 infection and its complications in children

Praca doktorska

Promotor: Prof. dr hab. n. med. Przemko Kwinta

Pracę wykonano w Oddziale Chorób Infekcyjnych i Pediatrii

Szpitala Specjalistycznego im. Stefana Żeromskiego w Krakowie.

Kierownik jednostki: Dr n. med. Jerzy Friediger

Podziękowania

Mojemu promotorowi, Prof. dr. hab. Przemkowi Kwincie dziękuję za cierpliwość, wyrozumiałość i życzliwość przekraczającą wszelkie oczekiwania.

Panu Dyrektorowi Dr. n. med. Jerzemu Friedigerowi dziękuję za wsparcie i nieustanne wskazywanie dalszych kierunków.

Spis treści

1. PUBLIKACJE ZAWARTE W ROZPRAWIE DOKTORSKIEJ

Rozprawa doktorska powstała w oparciu o monotematyczny cykl trzech artykułów opublikowanych w międzynarodowych czasopismach naukowych indeksowanych w bazie PubMed oraz znajdujących się na liście Journal Citation Reports (Thomson Reuters) o łącznej wartości współczynnika oddziaływania (IF) równym 13,635 oraz 380 punktów według wykazu czasopism naukowych Ministerstwa Nauki i Szkolnictwa Wyższego. We wszystkich artykułach jestem pierwszym autorem.

Prace wchodzące w skład cyklu powstały w oparciu o analizę przebiegu COVID-19 u pacjentów hospitalizowanych w Oddziale Chorób Infekcyjnych i Pediatrii Szpitala Specjalistycznego im. Stefana Żeromskiego w Krakowie oraz w Uniwersyteckim Szpitalu Dziecięcym Collegium Medicum Uniwersytetu Jagiellońskiego.

Na rozprawę doktorską składają się następujące artykuły:

I Artykuł nr 1

Characteristics of Hospitalized Pediatric Patients in the First Five Waves of the COVID-19 Pandemic in a Single Center in Poland—1407 Cases

Lidia Stopyra, Aleksandra Kowalik, Justyna Stala, Ida Majchrzak, Justyna Szebla, Mateusz Jakosz, Karolina Grzywaczewska, Przemko Kwinta

Journal of Clinical Medicine

Charakterystyka merytoryczna: praca oryginalna

(IF 4,964; MNiSW 140 punktów)

Wkład: opracowanie koncepcji pracy, określenie metodologii, przeprowadzenie badania, rekrutacja pacjentów do badania, zbieranie danych, analiza i interpretacja uzyskanych wyników, napisanie manuskryptu, autor korespondencyjny.

Mój udział procentowy szacuję na 65%.

Uzyskałam zgodę wszystkich współautorów na wykorzystanie pracy.

II Artykuł nr 2

The Age-Related Course of COVID-19 in Pediatric Patients—1405 Cases in a Single Center

Lidia Stopyra, Aleksandra Kowalik, Justyna Stala, Ida Majchrzak, Justyna Szebla, Mateusz Jakosz, Przemko Kwinta

Journal of Clinical Medicine

Charakterystyka merytoryczna: praca oryginalna

(IF 4,964; MNiSW 140 punktów)

Wkład: opracowanie koncepcji pracy, określenie metodologii, przeprowadzenie badania, rekrutacja pacjentów do badania, zbieranie danych, analiza i interpretacja uzyskanych wyników, napisanie manuskryptu, autor korespondencyjny.

Mój udział procentowy szacuję na 70%.

Uzyskałam zgodę wszystkich współautorów na wykorzystanie pracy.

III Artykuł nr 3

Risk factors of severe course and fatality in children hospitalized for COVID-19 – two centers cohort study.

Lidia Stopyra, Aleksandra Kowalik, Łukasz Wentrys, Przemko Kwinta

Archives of Medical Science

Charakterystyka merytoryczna: praca oryginalna

(IF 3,707; MNiSW 100 punktów)

Wkład: opracowanie koncepcji pracy, określenie metodologii, przeprowadzenie badania, rekrutacja pacjentów do badania, zbieranie danych, analiza i interpretacja uzyskanych wyników, napisanie manuskryptu, autor korespondencyjny.

Mój udział procentowy szacuję na 75%.

Uzyskałam zgodę wszystkich współautorów na wykorzystanie pracy.

Łączna wartość merytoryczna cyklu prac IF 13,635; MNiSW 380 punktów.

Dwa pierwsze artykuły zostały już opublikowane w czasopiśmie *Journal of Clinical Medicine*. Artykuł nr 3 został 3 czerwca 2023 roku zaakceptowany do publikacji w czasopiśmie *Archives of Medical Science* i został w niniejszej pracy wklejony w takiej formie, w jakiej został zaakceptowany do publikacji. Dołączona została decyzja o akceptacji.

2. WPROWADZENIE

W grudniu 2019 r. w Wuhan, w prowincji Hubei w Chinach, zanotowano pierwsze przypadki ciężkiego zapalenia płuc z niewydolnością oddechową, obarczonego znaczną śmiertelnością [1]. 9 stycznia 2020 r. ogłoszono, że w materiale pochodzącym z dróg oddechowych chorych wykryto nowy rodzaj wirusa, w lutym nowy wirus został zidentyfikowany i z racji podobieństwa genetycznego z SARS-CoV (severe acute respiratory syndrome coronavirus), który wywołał epidemię w 2003 r., został nazwany SARS-CoV-2. Chorobę wywoływaną przez SARS-CoV-2 nazwano COVID-19 (coronavirus disease 2019). 11 marca w związku z błyskawicznym rozprzestrzenianiem się wirusa WHO ogłosiła pandemię COVID-19 [2]. Z czasem okazało się, że wirus nie tylko charakteryzuje się olbrzymim potencjałem pandemicznym, ale również szybko mutuje. Większość mutacji wywoływała niewielki wpływ na przebieg kliniczny choroby, ale z czasem pojawiły się warianty wirusa wpływające na zwiększenie zakaźności i ciężkości zakażenia. 31 maja 2020 r. wprowadzono nomenklaturę wariantów wywodzącą się od liter alfabetu greckiego i kwalifikację wariantów wymagających szczególnego nadzoru epidemiologicznego VOC (variant of concern) [3].

Początkowo jako główne objawy COVID-19 podawano kaszel, gorączkę i duszność, ale szybko okazało się, że symptomatologia zakażenia jest znacznie bogatsza. Raportowano objawy nieżytu żołądkowo-jelitowego, zapalenie krtani, objawy neurologiczne, ale również typowe dla COVID-19 zaburzenia węchu i smaku. Mimo tego kliniczne rozpoznanie COVID-19 było praktycznie niemożliwe. Dane odnoszące się do pierwszego „dzikiego" wariantu wirusa mówiły o łagodnym przebiegu zakażenia u 40% chorych, średnim również u 40%, 15% chorych wymagało suplementacji tlenu, 5% rozwijało objawy niewydolności oddechowej, ARDS, posocznicy, wstrząsu septycznego, rozsiane wykrzepianie wewnątrznaczyniowe, niewydolność krążenia i niewydolność nerek [4]. Śmiertelność w COVID-19 oceniano na 2–5%. Taka sytuacja jest epidemiologicznie niezwykle niebezpieczna, gdyż wysoka liczba (80%) zakażonych z łagodnymi i niewielkimi objawami powoduje, że nie są oni skutecznie diagnozowani i izolowani, w związku z czym dochodzi do błyskawicznego rozprzestrzeniana się choroby, natomiast stosunkowo niewysoka śmiertelność przy wysokiej zakaźności przekłada się na wiele ofiar pandemii. Finalnie w ciągu 3 lat zaraportowano ponad 6,5 miliona zgonów [5], natomiast rzeczywistą liczbę zgonów z powodu COVID-19 szacuje się na co najmniej 20 milionów [6].

Taka sytuacja epidemiologiczna wymusiła konieczność znalezienia szybkich rozwiązań przede wszystkim w zakresie właściwej diagnostyki, zarówno w aspekcie skutecznych testów identyfikujących zakażenie, jak i rozwiązań organizacyjnych, oraz określenia zasad testowania, kwarantanny i izolacji. Ruszyły również intensywne prace zmierzające do wynalezienia leków przeciw SARS-CoV-2 oraz szczepionek przeciw COVID-19. W związku z tym ważne stało się jak najszybsze opisanie przebiegu zakażenia, możliwości rozpoznania klinicznego, określenie grup ryzyka ciężkiego przebiegu i zgonu, jak również zasad leczenia i wskazań do hospitalizacji oraz do profilaktyki. Ze względu na to, że pojawiły się pierwsze doniesienia, że przebieg zakażenia zależy od wielu czynników – jak np. wiek, choroby współistniejące, ale również czynniki genetyczne i np. przynależność etniczna, ważne stało się badanie przebiegu COVID-19 w każdej populacji. Ponadto ze względu na szybkie mutacje SARS-CoV-2 i powstawanie nowych wariantów wirusa o zwiększonej zakaźności i patogenności konieczne stało się sprawne aktualizowanie danych. Została opublikowana rekordowa liczba prac na temat jednej choroby – wg danych WHO ukazało się 721 621 publikacji [7].

Od początku pandemii dzieci były traktowane jako grupa niestanowiąca problemu w pandemii, początkowo pojawiały się nawet doniesienia, że dzieci nie odgrywają istotnej roli nawet w przenoszeniu zakażenia [8]. Raportowano, że dzieci stanowią zaledwie 1–2% zakażonych SARS-CoV-2, a przebieg zakażeń jest u nich asymptomatyczny lub łagodny. Z czasem jednak okazało się, że liczba dzieci z cięższym przebiegiem i hospitalizowanych zaczęła wzrastać [9]. Mało było publikacji na temat przebiegu COVID-19 u dzieci: w trakcie całej pandemii tylko ok. 5,5% opublikowanych prac na temat COVID-19 dotyczyło dzieci [7]. W pierwszym okresie tych doniesień praktycznie nie było. W maju 2020 r. pojawiły się pierwsze wiadomości o pojawieniu się ostrego powikłania zakażenia SARS-CoV-2 u dzieci, nazwanego PIMS-TS (pediatric inflammatory multisystem syndrome temporally associated with SARS-CoV-2) lub MIS-C (multisystem inflammatory syndrome in children) [10]. Z czasem, wraz z wprowadzeniem szczepień i zarejestrowaniem leków przeciwwirusowych u dorosłych, jak również w związku z uzyskaniem odporności populacyjnej, COVID-19 w dużej mierze stał się chorobą wieku dziecięcego.

Od początku pandemii, gdy Oddział Chorób Infekcyjnych i Pediatrii Szpitala im. Stefana Żeromskiego w Krakowie został zobowiązany decyzją Wojewody Małopolskiego do objęcia leczeniem pacjentów z COVID-19, rozpoczęto badanie zmierzające do określenia przebiegu

choroby i skuteczności wdrażanych metod postępowania. W trakcie 3 lat pandemii hospitalizowano około 3 tysięcy pacjentów z powodu COVID-19.

Dane dotyczące tak dużej liczby pacjentów hospitalizowanych w jednym ośrodku, ze spójną oceną, jak również jednolicie określonym postępowaniem, stanowią istotną podstawę do podejmowania decyzji diagnostycznych i terapeutycznych, tym bardziej że ze względu na odmienny przebieg zakażenia w różnych populacjach nie jest właściwe bezpośrednie ekstrapolowanie zaleceń z innych krajów czy też z populacji dorosłych.

3. STRESZCZENIE PRACY

3.1. Wstęp

11 marca 2020 r. Światowa Organizacja Zdrowia (WHO) ogłosiła pandemię COVID-19 (coronavirus disease 2019). W ciągu pierwszych trzech lat pandemii do WHO zgłoszono ponad 6,5 miliona zgonów z powodu tej choroby, ale zgłoszenia te pochodziły głównie z Europy i Ameryki Północnej. Ocenia się, że rzeczywista liczba zgonów była około trzykrotnie większa.

Od początku pandemii z całego świata napływały doniesienia, że przebieg zakażenia SARS-CoV-2 u dzieci jest bezobjawowy lub objawy są łagodne. Dzieci stanowiły 1–2% pacjentów z COVID-19 i rzadko wymagały hospitalizacji. Niemniej w kolejnych latach, wraz z pojawieniem się bardziej zakaźnych wariantów wirusa oraz wprowadzeniem szczepień u dorosłych, procent ten zaczął wzrastać. Pojawiły się też doniesienia o zgonach u dzieci.

Spowodowało to konieczność ścisłego monitorowania sytuacji epidemiologicznej, jak i opracowywania bieżących wytycznych dotyczących postępowania z pacjentami pediatrycznymi z COVID-19, a także identyfikacji grup ryzyka, kryteriów testowania i określania wskazań do hospitalizacji.

3.2. Cel badań, problemy badawcze

Głównym celem prowadzonych badań był opis przebiegu COVID-19 u hospitalizowanych dzieci w zakresie obrazu klinicznego, wyników badań laboratoryjnych, zmian w kolejnych falach pandemii i następstw zakażenia, przeprowadzony na podstawie danych pochodzących od ponad 1400 pacjentów pediatrycznych.

Na podstawie zebranych danych podjęto próbę odpowiedzi na następujące szczegółowe pytania badawcze:

1. Jakie były zmiany przebiegu choroby u dzieci w kolejnych falach pandemii, jako że obraz kliniczny zmieniał się w zależności od cech kolejnych wariantów wirusa oraz rosnącej odporności populacyjnej.
2. Czy były różnice w przebiegu COVID-19 zależne od wieku pacjentów, gdyż od początku pandemii we wszystkich doniesieniach podnoszono, że wiek jest najważniejszym czynnikiem ryzyka ciężkiego przebiegu, hospitalizacji i zgonu z powodu COVID-19.

Zostało to wielokrotnie potwierdzone u dorosłych, natomiast nie było takie jednoznaczne u dzieci.

3. Czym charakteryzowali się pacjenci z najcięższym przebiegiem choroby. Szczególnie skupiono się na kwestii, czy możliwe jest przewidywanie ciężkości przebiegu COVID-19 u pacjentów pediatrycznych na podstawie danych zebranych przy przyjęciu do szpitala.

3.3. Badana populacja

Do badania byli włączani pacjenci w wieku 0–18 lat z potwierdzonym laboratoryjnie zakażeniem SARS-CoV-2 hospitalizowani w Oddziale Chorób Infekcyjnych i Pediatrii Szpitala Specjalistycznego im. Stefana Żeromskiego w Krakowie oraz w Uniwersyteckim Szpitalu Dziecięcym Collegium Medicum Uniwersytetu Jagiellońskiego. Wszyscy pacjenci prezentowali objawy COVID-19.

3.4. Definicje

Zakażenie SARS-CoV-2 było potwierdzone dodatnim wynikiem reakcji odwrotnej transkryptazy łańcuchowej polimerazy (RT-PCR). Od 30 października 2020 r. zaczęto stosować zgodnie z rekomendacjami testy antygenowe II generacji. Materiałem do badań ww. był wymaz z nosogardła. Badania przeprowadzono w certyfikowanych laboratoriach.

Ciężki przypadek COVID-19 rozpoznawano u pacjentów w wieku 0–18 lat z potwierdzonym zakażeniem SARS-CoV-2, z zapaleniem płuc wymagającym tlenoterapii (biernej lub mechanicznej) lub w przypadku pacjentów stosujących tlenoterapię przewlekle, wymagających zwiększonego zapotrzebowania na tlen. Pacjenci z wieloukładowym zespołem zapalnym (MIS-C) byli wykluczani z badania.

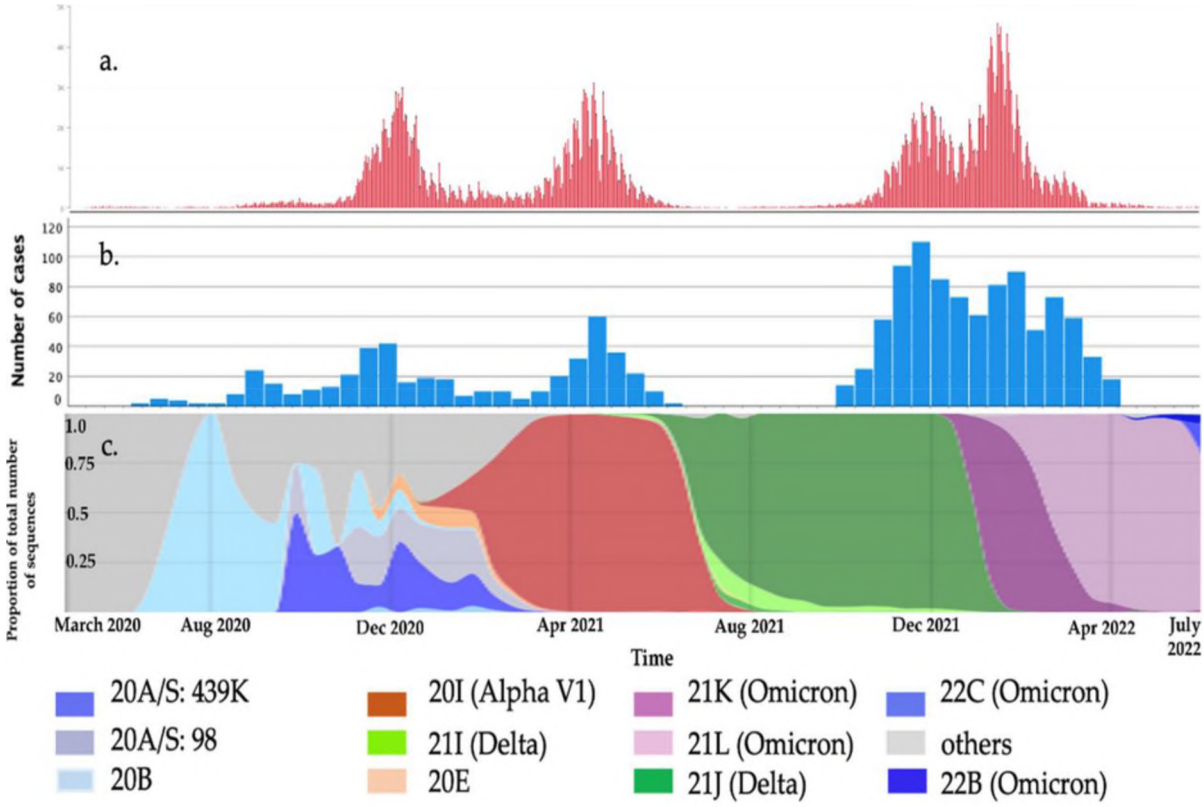
Kryteria przyjęcia do szpitala były podobne do stosowanych w innych infekcjach wieku dziecięcego, jak np. odwodnienie w przebiegu gorączki, wymiotów i biegunki, duszność, stan po drgawkach. Zgodnie z rekomendacjami Polskiej Grupy Ekspertów przyjmowano do szpitala również dzieci z chorobami współistniejącymi, takimi jak: wrodzone wady serca, choroby neurologiczne, genetyczne, przewlekłe choroby nerek, mukowiscydoza, dysplazja oskrzelowo-płucna, immunosupresja po przeszczepach narządowych i cukrzyca. Wg rekomendacji wśród pacjentów wymagających hospitalizacji były również noworodki, niemowlęta i dzieci z rozpoznaną otyłością, szczególnie z BMI powyżej 30 kg/m^2.

Dane każdego przyjmowanego pacjenta były wprowadzane do bazy wg standardowego protokołu. Przy przyjęciu zbierano wywiad, przeprowadzano badanie fizykalne i pobierano standardowy komplet badań identyczny dla wszystkich pacjentów: morfologię, CRP, ALT, LDH, CK, ferrytynę, prokalcytoninę (PCT). Wszystkie dzieci z ciężkim przebiegiem COVID-19 miały wykonywane badania obrazowe: USG płuc, RTG klatki piersiowej lub HRCT. Wszystkie dzieci były objęte ścisłą obserwacją i były leczone zgodnie z aktualnymi rekomendacjami. Dane odnośnie do przebiegu hospitalizacji (długość hospitalizacji, czas tlenoterapii, leczenie przeciwwirusowe, sterydoterapia systemowa, hospitalizacja w oddziale intensywnej terapii, wentylacja mechaniczna i zgony) były gromadzone wg jednolitego schematu.

3.5. Materiał i metody (dotyczy artykułu 1)

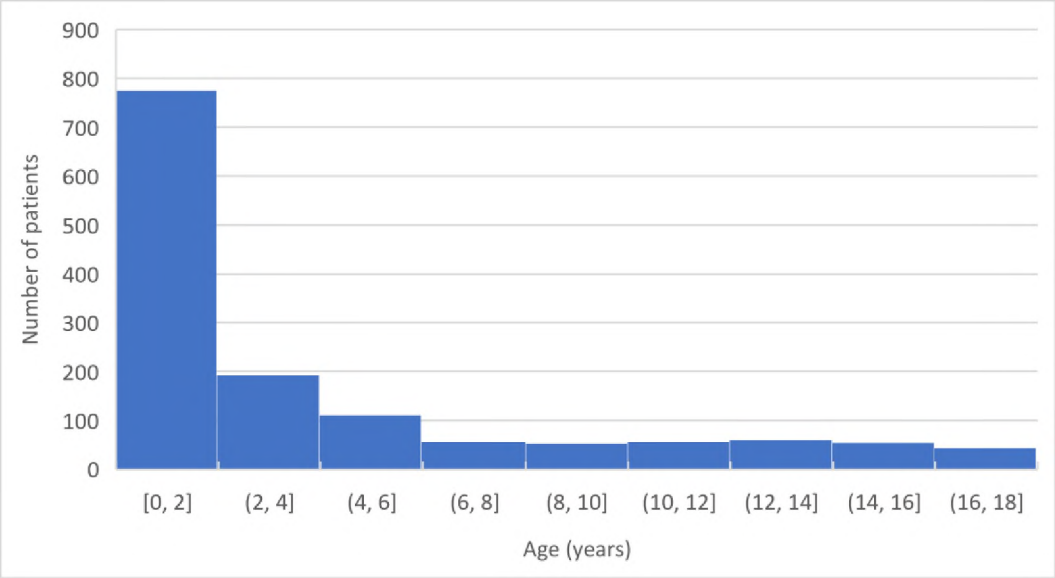
Badanie objęło 1407 pacjentów hospitalizowanych od marca 2020 r. do kwietnia 2022 r. w Oddziale Chorób Infekcyjnych i Pediatrii Szpitala Specjalistycznego im. Stefana Żeromskiego w Krakowie: 112 (8%) w pierwszej fali pandemii (od 1 marca do 30 września 2020 r.), 175 (12,4% w drugiej fali (od 1 października 2020 r. do 31 stycznia 2021 r.), 195 (13,8%) w trzeciej fali (od 1 lutego do 31 maja 2021 r.), 511 (36,3%) w czwartej fali (od 1 października 2021 r. do 15 stycznia 2022 r.) i 414 (29,5%) w piątej (od 16 stycznia do 30 kwietnia 2022 r.).

U pacjentów hospitalizowanych w kolejnych falach pandemii wywołanych przez różne warianty SARS-CoV-2 porównywano obraz kliniczny choroby, wyniki badań laboratoryjnych i obrazowych, przebieg zakażenia oraz diagnozy końcowe.



3.6. Materiał i metody (dotyczy artykułu 2)

Do badania zostało włączonych 1405 pacjentów z COVID-19, hospitalizowanych między marcem 2020 r. a kwietniem 2022 r. w Oddziale Chorób Infekcyjnych i Pediatrii Szpitala Specjalistycznego im. Stefana Żeromskiego w Krakowie. Aby ocenić przebieg choroby w zależności od wieku, pacjenci zostali podzieleni na 3 grupy: 567 niemowląt (0–12 miesięcy), 470 kilkulatków (1–5 lat) i 368 dzieci (5–18 lat). Obraz kliniczny, wyniki badań laboratoryjnych i obrazowych, dane o przebiegu choroby oraz diagnozy końcowe były porównywane między pacjentami z tych grup.



3.7. Materiał i metody (dotyczy artykułu 3)

70 spośród 2338 dzieci (3%) hospitalizowanych w dwóch ośrodkach od 23 marca 2020 r. do 30 września 2022 r. spełniło kryteria ciężkiego przebiegu COVID-19.

W pierwszej części badania szczegółowo opisano grupę dzieci z ciężkim przebiegiem COVID-19.

Następnie grupę dzieci z ciężkim przebiegiem COVID-19 na potrzebę dalszych analiz podzielono na 3 podgrupy:

1. dzieci, które nie wymagały wentylacji mechanicznej;
2. dzieci wymagające wentylacji mechanicznej;
3. dzieci, które zmarły z powodu COVID-19.

Na koniec przeprowadzono analizę porównującą grupę dzieci z ciężkim przebiegiem COVID-19 z dziećmi, które wymagały hospitalizacji, ale nie spełniły kryteriów ciężkiego przebiegu choroby.

3.8. Analiza statystyczna

Analizę statystyczną przeprowadzono za pomocą SPSS wersji 27 (Armonk, Nowy Jork, USA). Wyniki przedstawiono na podstawie parametrów statystyki opisowej, w tym wartości średnich i odchyleń standardowych (SD) dla zmiennych ilościowych o rozkładzie normalnym lub wartości median o rozstępie międzykwartylowym dla danych o rozkładzie innym niż normalny.

Zmienne kategoryczne przedstawiono w postaci liczb z procentami. Wartości jakościowe porównano za pomocą testu chi-square. Do analizy zmiennych ciągłych w badaniu wykorzystano test Kruskala-Wallisa. We wszystkich przypadkach istotności statystycznej przeprowadzono porównanie parami między grupami za pomocą testu post-hoc. We wszystkich analizach wartość $p < 0,05$ uznano za istotną statystycznie.

3.9. Etyka

Badanie zostało przeprowadzone zgodnie z wymogami etycznymi Deklaracji Helsińskiej z późniejszymi poprawkami. Badanie uzyskało zgodę Komisji Bioetycznej Okręgowej Izby Lekarskiej w Krakowie Nr OIL/KBL/18/2020 w dniu 10 marca 2020 r.

3.10. Podsumowanie wyników

3.10.1. Artykuł 1 opublikowany w Journal of Clinical Medicine

W tym badaniu przedstawiono wyniki analizy przebiegu COVID-19 w kolejnych pięciu falach pandemii u 1407 pacjentów, którzy spełnili kryteria włączenia.

Charakterystyka demograficzna pokazała niewielką przewagę chłopców we wszystkich pięciu falach pandemii bez istotnych różnic pomiędzy kolejnymi falami. Duże różnice zaobserwowano w wieku hospitalizowanych pacjentów. Średnia wieku była największa w pierwszej fali (95,8 miesięcy) i znacząco niższa w pozostałych, zmniejszając się stopniowo w kolejnych falach (w piątej średnia wieku wynosiła 14,6 miesiąca). Ciężkie przebiegi choroby u dzieci były rzadkie, bez istotnych różnic pomiędzy kolejnymi falami, niemniej obserwowano znaczące zwiększenie liczby hospitalizacji w czwartej i piątej fali. Choroby współistniejące były podobne u wszystkich pacjentów niezależnie od czasu zachorowania.

Główne różnice w obrazie klinicznym obejmowały zmiany w układzie oddechowym (katar, kaszel, duszność, zmiany osłuchowe nad polami płucnymi oraz zapalenie dolnych dróg oddechowych rozpoznawane na podstawie badań obrazowych), których częstość wzrastała od drugiej do czwartej fali pandemii. W przeciwieństwie do tego objawy ze strony układu pokarmowego (wymioty i biegunka) były najczęstsze w drugiej fali i w kolejnych nie wzrastały. Najwięcej objawów neurologicznych obserwowano w czwartej fali.

Jeśli chodzi o rozpoznania przy wypisie, to w piątej fali pandemii hospitalizowano najwięcej pacjentów z infekcją górnych dróg oddechowych (głównie z zapaleniem krtani) i objawami ze

strony przewodu pokarmowego, podczas gdy najwięcej infekcji dolnych dróg oddechowych występowało w pierwszej fali. W piątej fali stwierdzono więcej infekcji górnych niż dolnych dróg oddechowych i krótszy czas hospitalizacji.

Między pierwszymi pięcioma falami pandemii stwierdzono również istotne statystycznie różnice w wartościach badań laboratoryjnych w zakresie CRP, dehydrogenazy mleczanowej oraz liczby płytek krwi.

3.10.2. Artykuł 2 opublikowany w Journal of Clinical Medicine

Do badania oceniającego zależność pomiędzy przebiegiem COVID-19 a wiekiem dziecka włączono 1405 pacjentów. Wśród hospitalizowanych pacjentów obserwowano znaczną przewagę najmłodszych dzieci. Pacjenci w pierwszym roku życia stanowili 40,35%, a dzieci w wieku poniżej 5 lat 73,8% pacjentów pediatrycznych hospitalizowanych z powodu COVID-19.

Choroby współistniejące, związane ze zwiększonym ryzykiem ciężkiego przebiegu COVID-19, częściej występowały u dzieci powyżej piątego roku życia (42,3%).

Najczęściej stwierdzanymi objawami, szczególnie u pacjentów poniżej piątego roku życia, były gorączka, kaszel i katar. U dzieci poniżej pierwszego roku życia kaszel i duszność występowały głównie w przebiegu infekcji górnych dróg oddechowych, a najczęściej stawianą diagnozą było zapalenie krtani. Wysoka gorączka, wymioty i biegunka były najczęściej diagnozowane u pacjentów w wieku 0–5 lat, ale ostry nieżyt żołądkowo-jelitowy najczęściej rozpoznawano u pacjentów powyżej pięciu lat. Objawy neurologiczne występowały głównie u dzieci powyżej piątego roku życia.

W badaniach laboratoryjnych u większości pacjentów obserwowano leukopenię, neutropenię, limfocytozę, trombocytopenię i podwyższone wartości CRP, CK, LDH, ALT i D-dimerów, co jest typowe dla pacjentów z COVID-19, ale znacznie częściej występowało u dzieci poniżej piątego roku życia.

Średnia długość hospitalizacji wynosiła 3–4 dni i była znacząco większa wśród noworodków i niemowląt.

3.10.3. Artykuł 3 opublikowany w Archives of Medical Science

Spośród 2338 hospitalizowanych pacjentów pediatrycznych 70 spełniło kryteria ciężkiego przebiegu COVID-19 i zostało poddanych analizie.

W grupie pacjentów wymagających wentylacji mechanicznej odnotowano znaczącą przewagę tych z chorobami współistniejącymi, natomiast w grupie dzieci, które zmarły, wszystkie miały obciążenia. Najczęściej, podobnie jak w innych badaniach, obserwowano: schorzenia genetyczne, choroby neurologiczne, metaboliczne, kardiologiczne, otyłość, cukrzycę, przewlekłe choroby płuc, immunosupresję. W grupie dzieci wymagających wentylacji mechanicznej przy przyjęciu do szpitala częściej obserwowano kaszel i odwodnienie.

W zakresie badań laboratoryjnych stwierdzano wyższe wartości wskaźników zapalnych, limfopenię oraz trombocytopenię, a także wyższe poziomy ferrytyny i LDH. U dzieci, które zmarły, wartości wskaźników zapalnych LDH i ferrytyny były ekstremalnie wysokie. Również leukopenia i trombocytopenia były znacznie nasilone.

Wśród dzieci z ciężkim przebiegiem COVID-19 12% nie było szczepionych BCG, podczas gdy w grupie dzieci hospitalizowanych, które nie spełniły kryteriów ciężkiego przebiegu, tylko 3% było niezaszczepionych BCG.

Żadne z dzieci z ciężkim przebiegiem COVID-19 nie było zaszczepione przeciw COVID-19.

3.11. Wnioski

1. Przeprowadzone badania potwierdziły, że zagrażający życiu przebieg COVID-19 jest u dzieci stosunkowo rzadki. Niemniej dzieci z zapaleniem płuc, odwodnieniem w przebiegu gorączki, objawów żołądkowo-jelitowych i utraty smaku, jak również dzieci z objawami neurologicznymi często wymagały hospitalizacji. Liczba bezwzględna dzieci leczonych w szpitalu była znacząco wyższa w czwartej i piątej fali pandemii niż w pierwszych trzech falach. Przebieg kliniczny choroby zmieniał się pomiędzy marcem 2020 r. a kwietniem 2022 r., adekwatnie do pojawiania się nowych wariantów wirusa i wzrastającej odporności populacyjnej.

2. Wiele statystycznie istotnych różnic w obrazie klinicznym choroby obserwowano pomiędzy grupami wiekowymi. Najczęściej hospitalizowanymi pacjentami pediatrycznymi były niemowlęta. Wskazaniami do hospitalizacji najczęściej była konieczność nawadniania dożylnego w przebiegu odwodnienia w następstwie wysokiej gorączki, wymiotów, biegunki i zaburzeń łaknienia. Ciężkie przebiegi wymagające tlenoterapii i leczenia przeciwwirusowego były częstsze u nastolatków.

3. Czynnikami ryzyka ciężkiego przebiegu COVID-19 u pacjentów pediatrycznych były: młody wiek, brak szczepień BCG i przeciw COVID-19 oraz stwierdzane przy przyjęciu do szpitala duszność i zmiany osłuchowe nad polami płucnymi. Choroby współistniejące, wysokie CRP, LDH i ferrytyna były czynnikami ryzyka wentylacji mechanicznej i zgonu. Spośród dzieci wentylowanych mechanicznie nastolatkowie mieli większą szansę wyzdrowienia, natomiast niemowlęta z chorobami współistniejącymi były w grupie ryzyka zgonu.

Wyniki przeprowadzonego badania w dużej grupie ponad 1400 hospitalizowanych dzieci mogą być pomocne w formułowaniu zaleceń postępowania z dziećmi z COVID-19, określaniu grup ryzyka oraz zasad profilaktyki.

4. STRESZCZENIE PRACY W JĘZYKU ANGIELSKIM

4.1. Introduction

On 11 March 2020, the World Health Organization (WHO) announced the COVID-19 pandemic. In the first three years, over 6.5 million deaths for COVID-19 were reported to WHO, mainly from Europe and North America. The real number of deaths in the world is assessed to be three times larger.

From the beginning of the pandemic, children were reported all over the world to present with an asymptomatic or mild course of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection. Children were reported to constitute 1–2% of COVID-19 patients and it was very rare that admission to hospital was required. Nevertheless, during the following years, the percentage of hospitalization among children has increased since the emergence of more contagious (SARS-CoV-2) variants and the achievement of a high vaccination rate in adults. The first pediatric deaths were reported.

Such situation required thorough surveillance and ongoing update on COVID-19 management for children, and also risk group identification, testing criteria, and indications for hospitalization.

4.2. Research purpose, research problems

The main aim of the study was to describe the COVID-19 characteristics of hospitalized children based on findings from over 1400 pediatric patients, especially in terms of clinical presentation, laboratory findings, trends in pandemic waves, and outcomes.

Specifically, the following issues were analyzed:

1. What were the differences among the subsequent pandemic waves due to SARS-CoV-2 variants – because the clinical presentation of COVID-19 has been changing due to the following SARS-CoV-2 variants and raising herd immunity.
2. What was the relation between the course of pediatric COVID-19 and age – because from the beginning of the pandemic, age was reported as one of the most important risk factors for a severe course, hospitalization, and death due to COVID-19.

3. What were the characteristics of the patients with a severe course of the disease. Especially, I focused on the possibilities for prediction of the severity of COVID-19 on admission to the hospital.

4.3. Studied population

Patients aged 0–18 years with laboratory-confirmed COVID-19, hospitalized in the Department of Infectious Diseases and Pediatrics, Zeromski Specialist Hospital in Krakow, and The Children University Hospital, Jagiellonian University Collegium Medicum, Krakow, Poland were included in the study. All patients were symptomatic.

4.4. Definitions

SARS-CoV-2 infection was diagnosed using a positive reverse transcription and real-time polymerase chain reaction (RT-PCR) test. Since 30 October 2020, second-generation antigen tests from a nasopharyngeal swab were performed in certified laboratories.

The severe case was diagnosed in patients with pneumonia, age 0–18 years, laboratory-confirmed SARS-CoV-2 infection, and a new requirement for supplemental oxygen or increased requirement from baseline without new or increased need for ventilatory support (noninvasive or invasive). Patients diagnosed with Multisystem Inflammatory Syndrome in Children (MIS-C) were excluded.

Criteria for hospital admission were similar to other pediatric infectious diseases, such as dyspnea, seizures, dehydration from fever, vomiting, and diarrhea. According to Polish Expert Group recommendations, hospital referrals were also required for children with congenital heart defects, neurologic diseases, genetic disorders, chronic renal diseases, mucoviscidosis, broncho-pulmonary dysplasia, immunodeficiency after organ transplantation, and diabetes mellitus. Included also were newborns, infants, and children with obesity, especially with a body mass index (BMI) >30 kg/m^2.

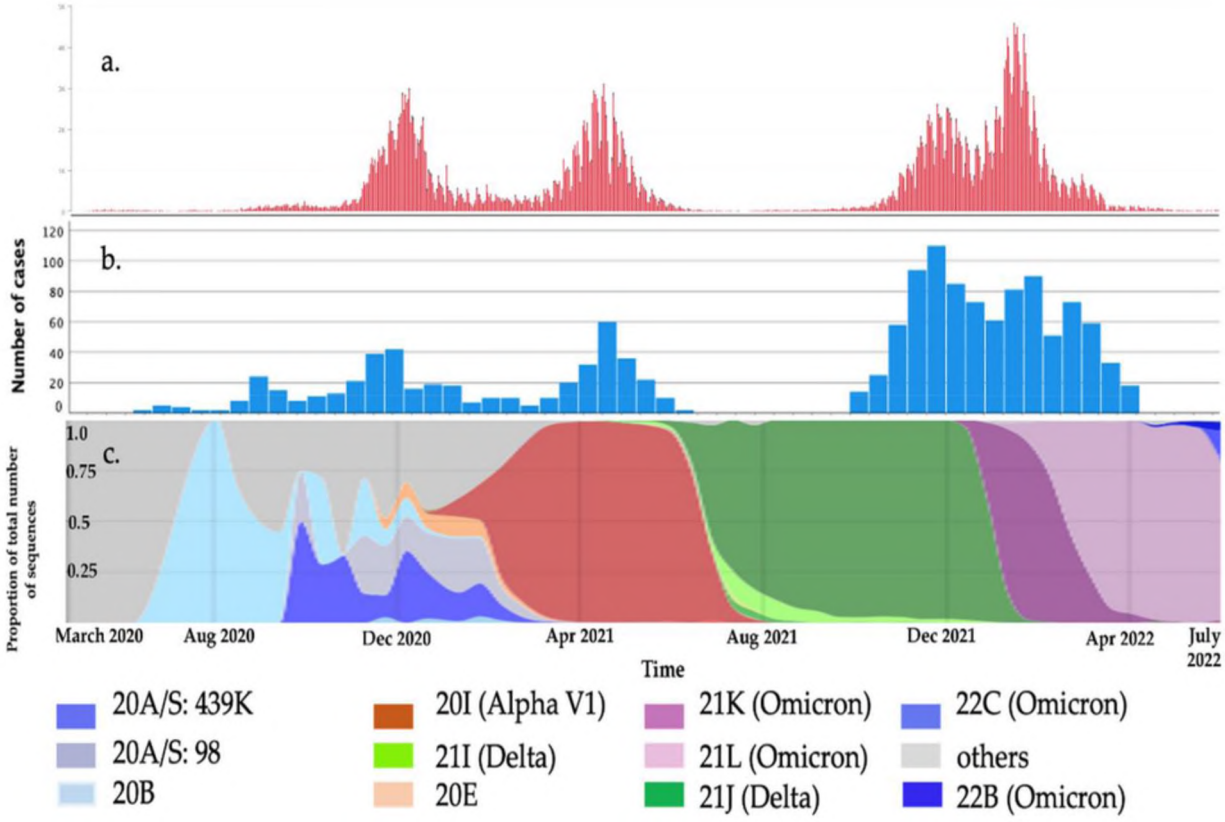
Data were collected in all successively admitted patients, based on a standard protocol. On admission, after taking the medical history and performing a physical examination, a planned set of laboratory tests was taken in all patients, including complete blood count (CBC) parameters, C-reactive protein (CRP), alanine transaminase (ALT), lactate dehydrogenase (LDH), creatine kinase (CK), ferritin, procalcitonin (PCT). All children with severe course of

COVID-19 had imaging tests taken (i.e., lung ultrasound (LU), chest X-ray, and high-resolution computed tomography (HRCT)). All children were subject to careful medical observation and treatment in accordance with current guidelines. Data on the course of hospitalization was also recorded in a planned and strictly structured manner in a specially designed database (the length of hospitalization, the length of oxygen treatment, antiviral treatment, systemic steroid therapy, pediatric intensive care unit (PICU) admission, respiratory therapy, and deaths).

4.5. Patients and methods (applies to article No 1)

This study comprised 1407 patients with COVID-19, hospitalized between March 2020 and April 2022 in the Department of Infectious Diseases and Pediatrics, Zeromski Specialist Hospital in Krakow: 112 (8%) from the first wave (1 March to 30 September 2020), 175 (12.4%) from the second (1 October 2020 to 31 January 2021), 195 (13.8%) from the third (1 February to 31 May 2021), 511 (36.3%) from the fourth (1 October 2021 to 15 January 2022), 414 (29.5%) from the fifth (16 January to 30 April 2022).

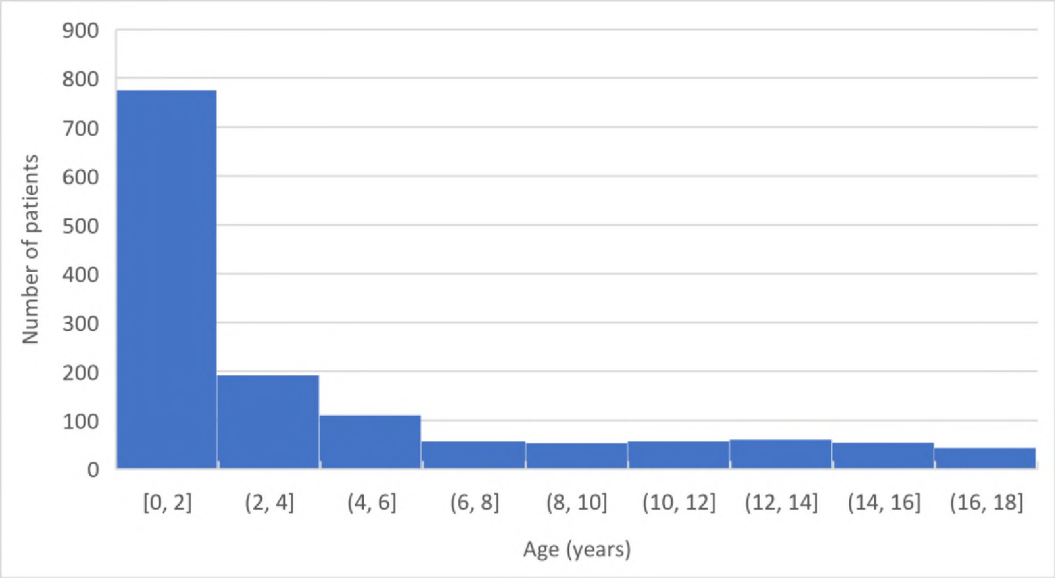
Demographic characteristics, clinical presentation, laboratory findings, lung imaging, outcomes, and final diagnoses were compared between the subsequent pandemic waves caused by different SARS-CoV-2 variants.



4.6. Patients and methods (applies to article No 2)

1405 patients with COVID-19 hospitalized between March 2020 and April 2022 in the Department of Infectious Diseases and Pediatrics, Zeromski Specialist Hospital in Krakow were included in the study. To assess the COVID-19 characteristics depending on age, they were assigned to three study groups: 567 infants (0–12 months), 470 toddlers (1–5 years), and 368 children (5–18 years).

Demographic characteristics, clinical presentation, laboratory findings, lung imaging, outcomes, and final diagnoses were compared between the age groups.



4.7. Patients and methods (applies to article No 3)

70 among 2338 children (3%) hospitalized in two centers between 23 March 2020 and 30 September 2022 met the criteria of COVID-19 severe course.

In the first stage of the analysis, the population of children with severe COVID-19 was described in detail.

Next, among children diagnosed with severe COVID-19, the following subgroups of patients were identified for further analysis:

1) children who did not require mechanical ventilation;

2) children requiring mechanical ventilation;

3) children who died due to severe COVID-19.

In the final stage of the analysis, the data of children with severe COVID-19 was also compared with the data of children who were hospitalized due to COVID-19, but did not meet the criteria for severe COVID-19.

4.8. Statistical analysis

The statistical analysis was performed using SPSS ver. 27 software (Armonk, NY, USA). Results were presented based on the parameters of descriptive statistics, including the mean values and standard deviations (SD) for the quantitative variables with a normal distribution or median values with the interquartile range for non-normally distributed data. Categorical variables were presented as numbers with percentages. Qualitative values were compared by the chi-square test. The Kruskal–Wallis test was used for the analysis of the continuous variables investigated in the study. In all cases of statistical significance, a pairwise comparison between the groups was performed using a post-hoc test. In all analyses, a p-value < 0.05 was considered statistically significant.

4.9. Ethics

The study was performed in accordance with the ethical standards of the Declaration of Helsinki and its later amendments. It was approved by the Ethics Committee of the Regional Medical Chamber in Krakow No OIL/KBL/18/2020 on 10 March 2020.

4.10. Summary of the results

4.10.1. Article No 1 published in Journal of Clinical Medicine

In the study, results of data analysis of the COVID-19 course in the first five waves of the pandemic, obtained from 1407 patients who met the inclusion criteria, were presented.

The demographic characteristics showed a slight prevalence of boys in all five waves. Significant differences in the age of patients were found between the following pandemic waves. The median age was the highest in the first wave (95.8 months) and significantly lower in others, decreasing in the following waves (it was 14.6 months in the fifth wave). Severe courses of the disease were rare, and there were no significant differences in severity between the five waves, although we did observe increased hospitalizations in the fourth and fifth waves. The comorbidities were similar.

The basic differences in the clinical presentation were the frequency of respiratory symptoms (rhinitis, cough, dyspnea, auscultatory changes, and lower respiratory infection diagnosed by imaging), which increased from the second to the fourth waves. In contrast, gastrointestinal symptoms (vomiting and diarrhea) were the most common in the second wave. More neurological symptoms occurred in the fourth wave.

Regarding the final diagnoses of the hospitalized COVID-19 pediatric patients, the number of children with upper respiratory or gastroenterological symptoms was the highest in the fifth wave, while that of lower respiratory infection was most common in the first wave. We observed more upper than lower respiratory infections and shorter lengths of stay in the hospital in the fifth wave.

Statistically significant differences in the first five waves of the pandemic in terms of CRP, blood platelets, and lactate dehydrogenase were found.

4.10.2. Article No2 published in Journal of Clinical Medicine

In this study, concerning the relation between the course of COVID-19 and the child's age, 1405 patients met the inclusion criteria. The large predominance of the youngest children were observed. Patients in the first year of life constituted 40.35% of the sample, and children younger than five years accounted for 73.8% of the hospitalized patients with COVID-19.

Comorbidities associated with the increased risk of severe disease mainly affected children older than five years (42.3%).

The most frequent symptoms were fever, cough, and rhinitis, especially in infants and toddlers. In infants, cough and dyspnea were more common symptoms of upper respiratory tract infection, and the most common diagnosis was laryngitis. High fever, vomiting, and diarrhea were observed much more frequently in patients aged 0–5 years, but gastroenterocolitis in our cohort was diagnosed as most common in children older than five years. Neurologic symptoms were significantly more common in the group of children older than five years.

Regarding to laboratory findings, we observed leucopenia, neutropenia, lymphocytosis, thrombocytopenia, and elevated CRP, CK, LDH, ALT, and D-dimers as typical in most pediatric patients with COVID-19, especially in patients 0–5 years old.

The median length of hospitalization in our cohort was 3–4 days and was significantly longer in the group of infants.

4.10.3. Article No 3 published in Archives of Medical Science

70 among 2338 hospitalized pediatric patients met the severity criteria established for the study and were enrolled in the analysis.

In the group of patients requiring invasive oxygen treatment the prevalence of those with underlying conditions was significant, and 100% of children who died because of COVID-19 had comorbidities. The most often were the same as in other studies – genetic conditions, neurologic conditions, metabolic conditions, cardiovascular disease, obesity, diabetes mellitus, chronic pulmonary diseases, immunosuppression. Children who required mechanical ventilation manifested cough and dehydration on admission more often.

As regards laboratory results, higher markers of inflammation, lymphopenia, and thrombocytopenia with higher concentrations of ferritin and LDH were observed. In children who died because of COVID-19 inflammation markers, leucopenia, thrombocytopenia, LDH, and ferritin level were extremely high.

The lack of BCG vaccination was found in 12% of children with severe COVID-19 and 3% in other hospitalized children.

None of the children with severe course of COVID-19 were vaccinated against COVID-19.

4.11. Conclusions

1. The study confirmed that a life-threatening course of COVID-19 in children was relatively rare. However, children with pneumonia, dehydration from fever, gastrointestinal symptoms, and loss of smell and taste, as well as those with neurological symptoms, represented most of the patients requiring hospitalization.

   The absolute number of hospitalizations was significantly higher in the fourth and fifth waves than in the first three waves. The clinical course of the disease changed between March 2020 and April 2022 due to the predominance of different SARS-CoV-2 variants and raising herd immunity.

2. Many statistically significant differences in disease signs and symptoms were observed between age groups. Infants were the most often hospitalized patients in the first two years of the pandemic. The reasons for infant hospitalization were the necessity of intravenous rehydration because of dehydration in the course of high fever, vomiting and diarrhea, and appetite disorders.

   Severe courses requiring oxygen supplementation and antiviral therapy were more common in adolescents.

3. Risk factors for the severe course of COVID-19 were: young age, lack of COVID-19 and BCG vaccination, auscultation changes, and dyspnea on admission.

   The presence of comorbidities, high CRP, LDH, and ferritin levels were the predictors of mechanical ventilation necessity and death. Among children mechanically ventilated teenagers were the patients with a prognosis of recovery, but infants with comorbidities were at the highest risk of death.

My observations of the large group including over 1400 hospitalized children may be useful for defining the high-risk group for severe COVID-19 and could help to guide hospital admission and prevention of COVID-19 in pediatric patients.

5. PIŚMIENNICTWO

1. Zhu N et al. (2020). A novel coronavirus from patients with pneumonia in China. *New England Journal of Medicine* 382, 727–733.
2. https://www.who.int/docs/default-source/coronaviruse/situation-reports/20200121-sitrep-1-2019-ncov.pdf; dostęp 23 maja 2023 r.
3. https://www.who.int/news/item/31-05-2021-who-announces-simple-easy-to-say-labels-for-sars-cov-2-variants-of-interest-and-concern; dostęp 23 maja 2023 r.
4. https://www.gov.uk/government/publications/wuhan-novel-coronavirus-background-information/wuhan-novel-coronavirus-epidemiology-virology-and-clinical-features; dostęp 23 maja 2023 r.
5. https://covid19.who.int/; dostęp 23 maja 2023 r.
6. https://www.who.int/data/stories/the-true-death-toll-of-covid-19-estimating-global-excess-mortality; dostęp 23 maja 2023 r.
7. https://search.bvsalud.org/global-literature-on-novel-coronavirus-2019-ncov/; dostęp 23 maja 2023 r.
8. Rajmil L. Role of children in the transmission of the COVID-19 pandemic: a rapid scoping review. *BMJ Paediatr Open*. 2020 Jun 21;4(1):e000722. doi: 10.1136/bmjpo-2020-000722. PMID: 32596514; PMCID: PMC7311007.
9. https://www.uptodate.com/contents/covid-19-clinical-manifestations-and-diagnosis-in-children; dostęp 23 maja 2023 r.
10. https://www.rcpch.ac.uk/sites/default/files/2020-05/COVID-19-Paediatric-multisystem-%20inflammatory%20syndrome-20200501.pdf; dostęp 23 maja 2023 r.

6. Publikacje

6.1. Publikacja pierwsza

Journal of
Clinical Medicine

MDPI

Article

Characteristics of Hospitalized Pediatric Patients in the First Five Waves of the COVID-19 Pandemic in a Single Center in Poland—1407 Cases

Lidia Stopyra [1,*], Aleksandra Kowalik [2], Justyna Stala [1], Ida Majchrzak [1], Justyna Szebla [1], Mateusz Jakosz [1], Karolina Grzywaczewska [1] and Przemko Kwinta [2]

[1] Department of Infectious Diseases and Pediatrics, Zeromski Specialist Hospital in Krakow, 30-931 Kraków, Poland
[2] Department of Pediatrics, Jagiellonian University Medical College, 30-663 Kraków, Poland
* Correspondence: lstopyra@zeromski-szpital.pl; Tel.: +48-126-229-513

Abstract: This is a single-center, prospective study that compared the clinical presentation and laboratory findings of hospitalized children during the first five waves of the COVID-19 pandemic. Data were collected, according to a standardized questionnaire, from 1407 children from 23 March 2020 to 30 April 2022. Significant differences in clinical courses were found among the five waves probably due to different SARS-CoV-2 variants. The median age was 95.8 months in the first wave versus 14.6–23 months in the others. The number of patients with upper respiratory infection was the highest in the fifth wave (74.4% versus 43.8–56.9% in the others) and for lower respiratory infection in the first wave (50.0% versus 16.4–32.5%). Gastroenterocolitis was more common in the fifth wave (24.4% versus 8.9–16.5%); neurological diagnoses appeared more frequently in the fourth wave (16.6% versus 0.6–9.9%), while anosmia and ageusia were higher in the fifth wave (13% versus 1.5–4%). Life-threatening courses were relatively rare. However, children with pneumonia, dehydration from high fever, gastrointestinal symptoms, loss of smell and taste, and neurological symptoms required hospitalization.

Keywords: COVID-19; SARS-CoV-2; children; pandemic; waves; hospitalization; clinical presentation

Citation: Stopyra, L.; Kowalik, A.; Stala, J.; Majchrzak, I.; Szebla, J.; Jakosz, M.; Grzywaczewska, K.; Kwinta, P. Characteristics of Hospitalized Pediatric Patients in the First Five Waves of the COVID-19 Pandemic in a Single Center in Poland—1407 Cases. *J. Clin. Med.* **2022**, *11*, 6806. https://doi.org/10.3390/jcm11226806

Academic Editors: Shitij Arora and Leonidas Palaiodimos

Received: 23 September 2022
Accepted: 16 November 2022
Published: 17 November 2022

1. Introduction

In February 2020, the World Health Organization (WHO) designated a new strain of betacoronavirus as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the causative agent of coronavirus disease 2019 (COVID-19) [1]. Fever, cough, and dyspnea were initially indicated as the presenting symptoms of SARS-CoV-2 infection. Severe pneumonia with respiratory failure reported on 31 December 2019 in the region of Wuhan, China, was the reason for hospitalization and life-threatening situations [2].

In the first reports of COVID-19, the frequency of disease in children appeared much lower than in adults. Both in China and in Italy, only 1% of cases were pediatric [2,3]. In the following months, the number of pediatric patients gradually increased. For instance, in the U.S., at the beginning of the pandemic, 2.2–4.2% of the reported cases were pediatric; then, according to reports from the American Academy of Pediatrics (AAP), the rate increased to 14.3% and in 10 states, children accounted for over 18% of cases [4,5]. Data from the European Centre for Disease Prevention and Control (ECDC) showed that up to 17.6% of cases were pediatric [6]. A lot of studies published have confirmed the clinical impression that COVID-19 in children typically presents as a mild (37%) or moderate (45%) upper respiratory tract infection and is rarely severe or critical [7]. Other signs and symptoms described in children include gastrointestinal, anosmia, ageusia, neurological, and dermatologic manifestations [2,3,7–17].

Numerous SARS-CoV-2 variants have circulated globally since the beginning of the pandemic, and differences in their courses have been reported [1,4,10–12,16–29]. The increasing number of pediatric cases and changing clinical disease presentations might require changes in COVID-19 management for children, risk group identification, testing criteria, and indications for hospitalization.

The aim of this paper was to describe the COVID-19 characteristics in hospitalized Polish children during the first five waves and to assess whether there were any differences among the different waves. In particular, the trends in the demographic data, clinical presentation, laboratory findings, and COVID-19 outcomes over two years of the pandemic were analyzed. Our observations may be useful for ongoing guidance for the evaluation, management, and prevention of COVID-19 in children.

2. Materials and Methods

Because of the WHO's announcement of a pandemic and the increasing cases of COVID-19 in Poland, the Department of Infectious Diseases and Pediatrics was instituted to be the central unit for treating pediatric COVID-19 cases in the southern region. The first two children were admitted to hospital on 23 March 2020, which is when this study commenced. Every patient from 0 to 18 years of age with confirmed COVID-19 hospitalized between March 2020 and April 2022 was included.

Following the recommendations from the WHO and the National Institute of Public Health [30,31], COVID-19 was diagnosed using a positive reverse transcription and real-time polymerase chain reaction (RT-PCR) test. Since 30 October 2020, second-generation antigen tests from a nasopharyngeal swab were performed in certified laboratories. Several kits were used: (1) GeneFinder™ COVID-19 Plus RealAmp, Elitech, Biomedica (Oxford, UK); (2) Liferiver, Novel Coronavirus (2019-nCoV) Real Time Multiplex; (3) VIASURE CerTest, Biotec (Zaragoza, Spain); (4) Maccura SARS-CoV-2 Fluorescent PCR, Maccura Biotechnology (Sichuan, China); (5) Homemade DIAGtest SARS-CoV-2 real time RT-PCR; (6) Labsystems Diagnostics (Vantaa, Finland). COVID-19 Real Time Multiplex RT-PCR and the second-generation Abbott Panbio-COVID-19 Ag Rapid Test Device (WHO laboratory 2020, AOTM).

Criteria for hospital admission were similar to other pediatric infection diseases, such as dehydration from fever, vomiting, and diarrhea. According to the Polish Ministry of Health [32], hospitalization was compulsory for every patient with diagnosed SARS-CoV-2 infection up to September 2020. According to Polish expert group recommendations, hospital referrals were also required for children with congenital heart defects, neurologic diseases, genetic disorders, chronic renal diseases, mucoviscidosis, broncho-pulmonary dysplasia, immunodeficiency after organ transplantation, and diabetes mellitus. Included also were newborns, infants, and children with obesity, especially with a body mass index (BMI) >30 kg/m^2 [33].

Discharge criteria were two negative PCR tests taken within 24 h. After 2 September 2020, the only criterion was the condition of the patient.

The disease severity assessment in this analysis was based on the need for oxygen, intravenous rehydration or steroids, and the length of stay. Antiviral therapy was also assessed. Systemic steroid and antiviral therapy were used according to the recommendations from the beginning of the pandemic [33–39] with the following changes: Dexamethasone was used according to the European Medicines Agency's (EMA) recommendations in hospitalized patients, especially in those treated with remdesivir at a dose of 0.1 mg/kg for a maximum of 4 mg/24 h [34]. Dexamethasone was also used in some patients with laryngitis according to references from previous studies [40,41].

Remdesivir was used in our department according to the Food and Drug Administration's (FDA) and EMA's recommendations [35,42]. According to the product characteristics, remdesivir was used in patients 12 years of age and older weighing at least 40 kg. It was also used in pediatric patients weighing at least 3.5 kg with positive results for direct SARS-CoV-2 testing with pneumonia and requiring oxygen supplementation. Baricitinib

was used in patients aged 2–18 years who required non-invasive or invasive mechanical ventilation with recommended dosages under the Emergency Use Authorization (EUA): for patients aged nine years or older, 4 mg once daily, and for those aged two to less than nine years, 2 mg once daily [43]. Data were collected and reported by the physicians working in the department according to a standardized case history questionnaire and a physical examination for every patient. Symptoms were recorded at the time of hospitalization. Standard laboratory tests were conducted for every child diagnosed with COVID-19.

All patients included in the study were symptomatic. The questionnaire included:

1. Demographic data: age, sex, ethnicity, recent contact with patients with COVID-19, and comorbidities (e.g., heart, chronic lung, neurological, or genetic diseases; asthma; developmental delay; diabetes; immunodeficiency, or malignancy).
2. Signs and symptoms: fever, cough, rhinitis, dyspnea, sore throat, weakness, diarrhea, abdominal pain, vomiting, headache, conjunctivitis, nausea, myalgia, rash, ageusia, anosmia, chest pain, or irritability.
3. Disease outcome data: length of hospitalization, complications, oxygen treatment, casual treatment, pediatric intensive care unit (PICU) admission, or death.
4. Laboratory data: complete blood count (CBC) parameters, C-reactive protein (CRP), alanine transaminase (ALT), lactate dehydrogenase (LDH), creatinine kinase (CK), ferritin, vitamin D3 level, prothrombin time, D-dimers, nasal swabs for other viral pathogens (co-infection), and imaging (i.e., lung ultrasound (LU), chest X-ray, and high-resolution computed tomography (HRCT)).
5. Final diagnoses: Upper or lower respiratory tract infection, gastroenterocolitis, or neurological diagnoses.

Lower respiratory infections were diagnosed based on clinical presentation and LU, chest X-ray, and HRCT. The examination taken most often, especially in the youngest children, was LU. The presence of focal, multifocal, and confluent B lines and pleural irregularities were the most common LU findings for diagnosing pneumonia from COVID-19. In chest X-ray examinations, bilateral and multifocal lesions were found most frequently, especially in the lower lobes. The pure ground-glass appearance was also typical for COVID-19 lower respiratory-related findings [44–46]. Regarding gastrointestinal infection, diagnosis was based on clinical presentation (i.e., vomiting or diarrhea) and the exclusion of any other etiology such as rotavirus, adenovirus, and norovirus.

Statistical analysis was performed using SPSS ver. 27 software (Armonk, NY, USA). The results are presented based on the parameters of descriptive statistics, including either the mean value and standard deviation (SD) for the quantitative variables with normal distribution or the median value with the interquartile range in the opposite case. Categorical variables are presented as numbers with percentages. Qualitative values were compared using the chi-squared test. For the analysis of continuous variables, a Kruskal–Wallis test was used. In all cases of statistical significance, a pairwise comparison between groups was performed using a post hoc test. In all of the analyses, $p < 0.05$ was considered statistically significant.

This study was performed in accordance with the ethical standards of the Declaration of Helsinki and its later amendments. It was approved by the Ethics Committee of the Regional Medical Chamber in Krakow, No. OIL/KBL/18/2020, on 10 March 2020.

3. Results

We compared the data characteristics of those children and adolescents admitted with acute COVID-19 during the first five waves of the pandemic.

3.1. Study Groups

This study comprised 1407 patients: 112 (8%) from the first wave (1 March to 30 September 2020); 175 (12.4%) from the second (1 October 2020 to 31 January 2021); 195 (13.8%) from the third (1 February to 31 May 2021); 511 (36.3%) from the fourth (1 October

2021 to 15 January 2022); 414 (29.5%) from the fifth (16 January to 30 April 2022) (Figure 1). All but one of the children were white European; the other was of Asian background.

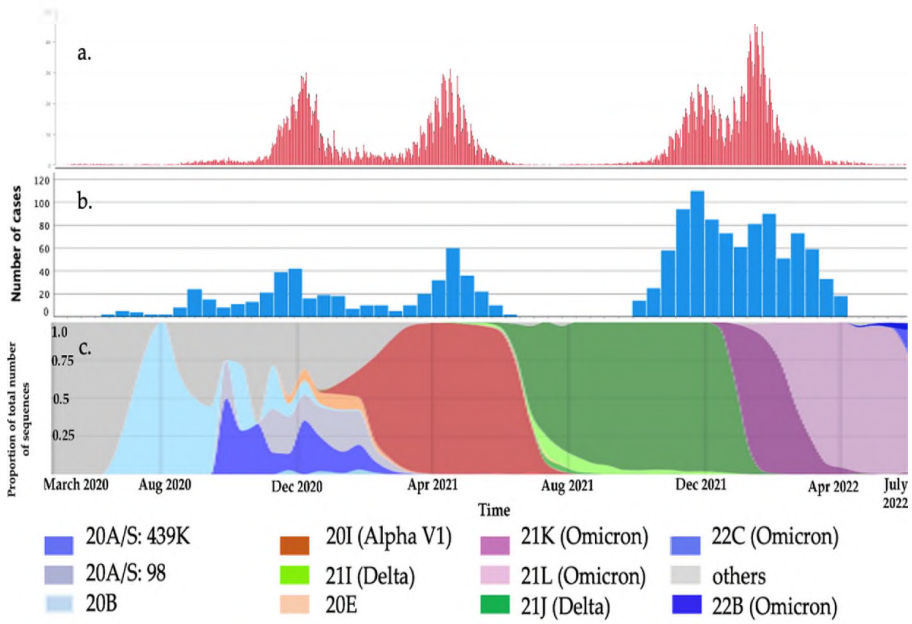


Figure 1. COVID-19 cases in our region: (**a**). Daily COVID-19 cases in the Malopolska region based on [47]. (**b**). Number of hospitalized children with COVID-19. (**c**). The proportion of the total number of SARS-CoV-2 variants over time in Poland based on [48].

Table 1 shows the demographic characteristics of the hospitalized patients.

Table 1. Demographic characteristics of those COVID-19 pediatric patients hospitalized during the first five waves of the pandemic.

	First Wave n = 112	Second Wave n = 175	Third Wave n = 195	Fourth Wave n = 511	Fifth Wave n = 414	p-Value	Post Hoc Analysis
Male sex, n (%)	57 (50.9)	99 (56.6)	100 (51.3)	258 (50.7)	228 (55.1)	0.569 *	
Age, months Median (25th–75th percentile)	95.8 (17–130)	23.0 (5.7–85)	20.1 (5.4–55)	17.6 (5.3–68)	14.6 (5.4–43)	<0.001 #	1 vs. 2: <0.001 1 vs. 3: <0.001 1 vs. 4: <0.001 1 vs. 5: <0.001
Patients with chronic diseases, n (%)	39 (34.8)	37 (21.1)	63 (32.3)	111 (21.7)	107 (26.8)	0.06 *	
Immunocompromised patients, n (%)	2 (1.9)	6 (3.5)	5 (2.6)	4 (0.8)	4 (1.0)	0.064 *	
BCG vaccinated patients, n (%)	97 (96)	159 (98)	178 (98)	483 (96)	399 (97)	0.59 *	

* Chi-squared test; # Kruskal–Wallis ANOVA.

In all waves, more boys than girls were hospitalized (from a low of 50.5% in the fourth wave to a high of 56.6% in the second), with no statistical significance between waves. The median age was the highest in the first wave (95.8 months) and significantly lower in others, decreasing in the following waves: 23 months in the second, 20.1 months

in the third, 17.6 months in the fourth, and 14.6 months in the fifth ($p < 0.001$). Chronic comorbidities, which related to high risk of severe COVID-19 were present in 21.1% of patients in the second wave to 34.8% in the first, and there were no statistically significant differences in the comorbidity frequency between waves ($p = 0.06$).

3.2. Clinical Presentation

The clinical presentation of pediatric COVID-19 during the first five waves of the pandemic is shown in Table 2.

Table 2. Clinical characteristics of those COVID-19 pediatric patients hospitalized during the first five waves of the pandemic.

	First Wave $n = 112$	Second Wave $n = 175$	Third Wave $n = 195$	Fourth Wave $n = 511$	Fifth Wave $n = 414$	p-Value *
Fever, *n* (%)	76 (69)	117 (67)	146 (75)	347 (68)	296 (71)	0.327
Rhinitis, *n* (%)	24 (21)	48 (28)	78 (40)	266 (52)	193 (47)	<0.001
Cough, *n* (%)	42 (38)	62 (36)	119 (61)	326 (64)	221 (53)	<0.001
Dyspnea, *n* (%)	11 (10)	13 (7.4)	24 (12)	73 (14)	46 (11)	0.143
Vomiting, *n* (%)	7 (6.3)	37 (21)	27 (14)	91 (18)	126 (30)	<0.001
Diarrhea, *n* (%)	22 (20)	54 (31)	39 (20)	91 (18)	105 (25)	0.002
Anosmia, *n* (%)	3 (2.7)	7 (4)	3 (1.5)	8 (1.6)	54 (13)	<0.001
Ageusia, *n* (%)	2 (1.8)	5 (2.9)	3 (1.5)	10 (2)	54 (13)	<0.001
Neurologic symptoms, *n* (%)	15 (14)	19 (11)	9 (4.6)	52 (10)	38 (9.2)	0.077

* Chi-squared test.

The most frequent symptom in all waves was fever. (68% in the fourth wave to 75% in the third), with no statistically significant differences between waves. The fever was defined as a temperature above 37.5 °C (99.5 °F) in axillary, ear, and forehead temperature measurements. In the case of respiratory symptoms, rhinitis was most frequently reported in the fourth wave (52% of patients), and significantly the least in the first (21%), whereas cough was most common in the third (61%) and fourth waves (64%) ($p < 0.001$). Dyspnea was a relatively rare symptom, although the study included only hospitalized patients—7.4% in the second wave to 14% in the fourth, with no statistically significant differences between waves.

In the case of gastrointestinal symptoms, vomiting was the rarest in the first wave (6.3%) and the most common in the fifth (30%) ($p < 0.001$), and diarrhea was the most common in the second wave (31% versus 18–25% in the others) ($p = 0.002$).

Anosmia and ageusia, the most specific COVID-19 symptoms, were rare in the children in the first four waves (1.5–4% of children), but the frequency of these symptoms was much higher in the fifth wave (13%) ($p < 0.001$).

Neurological manifestations (seizures and impaired coordination and balance) appeared in 4.6% of the patients in the third wave to 14% of the patients in the first wave, and the differences between waves were statistically insignificant. Table 2 shows the symptoms by wave.

3.3. Laboratory Findings

The laboratory findings from the children during the first five waves of the pandemic are shown in Table 3. There were no statistical differences between the groups at the CRP level or in the number of neutrophils, but there were differences between the waves in seven parameters. The number of leukocytes was the lowest in the first wave (median of 6.4 $\times$ $10^3/\mu L$) ($p < 0.001$), similar in the others (7.75–8.9 $\times$ $10^3/\mu L$). The number of lymphocytes was also the lowest in the first (median of 2.3 $\times$ $10^3/\mu L$ vs. 3.49, 3.96, 3.61, and 3.39 $\times$ $10^3/\mu L$ ($p < 0.001$) in waves 2–5, respectively). The first-wave patients also had the lowest platelet count (median of 247 vs. 309, 303, 279, and 281 $\times$ $10^3/\mu L$ in waves 2–5, respectively ($p < 0.001$). There were also differences in alanine transaminase and creatinine

kinase ($p < 0.001$), but the post hoc analysis revealed them to be significantly higher in the fifth wave.

Table 3. Laboratory findings in those COVID-19 pediatric patients hospitalized during the first five waves of the pandemic according to the Kruskal–Wallis and chi-squared tests.

	First Wave $n = 112$	Second Wave $n = 175$	Third Wave $n = 195$	Fourth Wave $n = 511$	Fifth Wave $n = 414$	p-Value	Post Hoc Analysis
CRP (mg/dL) (normal value = 0–5 mg/dL)	2.05 (1–9)	2.1 (1–12.6)	2.05 (1–14)	2.9 (1–10)	3.7 (1–11)	0.11 #	
CRP > 5 mg/dL	37 (38)	57 (38)	67 (36)	187 (38)	160 (41)	0.799 *	
Leukocytes ($10^3/\mu L$) (normal value = 6–10 × $10^3/\mu L$)	6.4 (5–8.1)	8.2 (6–11.6)	8.9 (6.1–12.5)	8.0 (5.8–11)	7.75 (5.9–11.2)	<0.001 #	1 vs. 2: <0.001 1 vs. 3: <0.001 1 vs. 4: <0.001 1 vs. 5: <0.001
Leukocytes ($10^3/\mu L$)							
<4.5	18 (18)	19 (13)	19 (10)	59 (12)	35 (9)		
4.5–13.5	79 (78)	106(69)	131(69)	368 (75%)	301(37)		
>13.5	4 (4)	27 (18)	39 (21)	63 (13)	54 (14)		
Neutrophils ($10^3/\mu L$) (normal value = 1.5–7 × $10^3/\mu L$)	2.89 (1.8–4.2)	2.62 (1.2–4.7)	2.62 (1.4–4.9)	2.59 (1.6–4.7)	2.7 (1.6–4.8)	0.925 #	
Neutrophils ($10^3/\mu L$)							
<1.0	7 (8)	26 (18)	29 (16)	65 (13)	45 (12)	0.016 *	
1.0–6.5	79 (87.6)	95 (64)	119 (68)	348 (74)	284 (73)		
>6.5	4 (4.4)	26 (18)	28 (16)	64 (13)	57 (15)		
Lymphocytes ($10^3/\mu L$) (normal value = 2.5–8.5 × $10^3/\mu L$)	2.3 (1.5–3.2)	3.46 (2.1–5.3)	3.96 (2.4–6.4)	3.61 (2.1–5.7)	3.39 (1.7–5.7)	<0.001 #	1 vs. 2: <0.001 1 vs. 3: <0.001 1 vs. 4: <0.001 1 vs. 5: <0.001
Lymphocytes ($10^3/\mu L$)							
<1.0	10 (11)	12 (8)	6 (3.4)	25 (5.3)	43 (11)	<0.001 *	
1.0–7.0	78 (26)	117 (80)	139 (77)	381 (80.4)	297 (75)		
>7.0	3 (3)	17 (12)	33 (19)	68 (14.3)	48 (24)		
Blood platelets ($10^3/\mu L$) (normal value = 210–560 × $10^3/\mu L$)	247 (192–298)	309 (247–411)	303 (243–360)	279 (215–363)	281 (222–351)	<0.001 #	1 vs. 2: <0.001 1 vs. 3: <0.001 1 vs. 4: 0.005 1 vs. 5: 0.01
Blood platelets < 100 × $10^3/\mu L$	4 (4)	3 (2)	3 (1.6)	10 (2)	3 (0.8)	0.265 *	
Alanine transaminase (U/L) (normal value = 0–55 U/L)	16 (12–24)	18 (12–28)	19 (13–29)	20 (13–29)	22 (15–32)	<0.001 #	5 vs. 1: <0.001 5 vs. 2: 0.015 5 vs. 3: 0.03 5 vs. 4: 0.017
Alanine transaminase >55 (U/L)	3 (3.2)	9 (6.3)	8 (4.5)	21 (4.5)	33 (8)	0.065 *	
Creatinine kinase (U/L) (normal value = 30–170 U/L)	80 (55–114)	84 (63–125)]	108 (71–157)	94 (65–146)	115 (83–168)	<0.001 #	5 vs. 1: <0.001 5 vs. 2: <0.001 5 vs. 4: <0.001
Creatinine kinase							
170 (U/L)	5 (9.4)	12 (12.5)	31 (19)	66 (15.3)	82 (24)	0.005 *	
Lactate dehydrogenase (IU/L) (normal value = 125–220 (U/L)	238.5 (192–293)	268.5 (210–311)	286.0 (236–323)	272.0 (221–313)	293.0 (252–333)	<0.001 #	1 vs. 3: <0.001 1 vs. 4: 0.023 1 vs. 5: <0.001 5 vs. 2: 0.001 5 vs. 4: <0.001
Lactate dehydrogenase >220 IU/L	51 (57)	101 (70)	148 (88)	316 (85)	280 (86)	<0.001 *	
D-dimers (ng/mL) (normal value = 0–500 ng/mL)	407 (256–694)	582 (377–1142)	471 (294–908)	559 (331–1082)	611 (397–1065)	<0.001 #	1 vs. 2: 0.004 1 vs. 4: 0.004 1 vs. 5: <0.001
D-dimers > 500 ng/mL	33 (38)	80 (60)	72 (47)	205 (54)	184 (61)	<0.001 *	

* Chi-squared test, data are presented as n (%); # Kruskal–Wallis ANOVA, data are presented as the median (25th–75th percentile).

The Kruskal–Wallis test showed significant differences between the groups in LDH level ($p < 0.001$); however, in the post hoc analysis, the first and fifth wave groups differed from the others. D-dimers were significantly lower in the first wave versus the second, fourth, and fifth waves ($p < 0.001$). In the chi-squared test, significant differences were found in the leukocyte ($p = 0.003$) and lymphocyte levels ($p < 0.001$), creatinine kinase ($p = 0.005$), and lactate dehydrogenase and D-dimers ($p < 0.001$).

3.4. COVID-19 Severity

The COVID-19 severity data are included in Table 4. Oxygen therapy was required in 0% (first wave) to 4% (fourth wave) of the patients and there were no statistically significant differences between the five waves ($p = 0.071$). Differences were found in the need for intravenous rehydration—most common in the fifth wave (59%) and least in the third wave (9%) ($p < 0.001$). Systemic steroid therapy was used the least in the second wave (1.1%) and the most in the fourth wave (11.2%) ($p < 0.001$). The length of stay was significantly shorter in the fifth wave (median of three days). The post hoc analysis revealed differences between the fifth and all other waves ($p < 0.001$). Only one (0.5%) patient in the third wave and two (0.3%) in the fourth were referred to a PICU, but no one died. One patient in our department needed high-flow nasal oxygen therapy (HFNOT). Nine (1.7%) patients in the fourth wave were treated with remdesivir (0.64% during the whole pandemic) and 1 (0.19%) with baricitinib according to FDA and EMA recommendations [25,30,31]. Two (0.4%) patients in the fifth wave were treated with baricitinib (0.21% during the whole pandemic).

Table 4. COVID-19 outcomes in those hospitalized pediatric patients during the first five waves of the pandemic.

	First Wave $n = 112$	Second Wave $n = 175$	Third Wave $n = 195$	Fourth Wave $n = 511$	Fifth Wave $n = 414$	p-Value	Post Hoc Analysis
Oxygen therapy, n (%)	0	2 (1.1)	8 (4)	19 (4)	9 (2.2)	0.071 *	
Intravenous fluids, n (%)	24 (21)	62 (35)	18 (9)	243 (48)	243 (59)	<0.001 *	
Steroid therapy, n (%)	7 (6)	2 (1.1)	18 (9)	57 (11.2)	20 (4.8)	<0.001 *	
Antiviral therapy, n (%)	0	0	0	10 (1.9) (remdesivir—9, baricitinib—1)	2 (0.4) (baricitinib—2)	0.67 *	
Length of stay, n (days) Median (25th–75th percentile)	4 (2–6)	4 (3–5)	3 (2–6)	4 (3–5)	3 (2–4)	<0.001 #	5 vs 1: <0.001 5 vs 2: <0.001 5 vs 3: <0.001 5 vs 4: <0.001

* Chi-squared test; # Kruskal–Wallis ANOVA.

3.5. Final Diagnoses

Because of the overlap, there were 1862 diagnoses in the 1407 patients, of whom 235 (16.7%) had more than one final diagnosis: urinary tract infection (UTI) combined with gastroenterocolitis, pneumonia and gastroenterocolitis, and upper respiratory tract infection and seizures or suicide attempts. In the first and second waves, there were 1.2 diagnoses per patient, but that increased in the following waves to 1.26 in the third, 1.35 in the fourth, and 1.39 in the fifth. The average for the whole period was 1.32. This means that through subsequent waves the symptomatology of COVID-19 in children was becoming richer.

The most common final diagnoses were upper respiratory, lower respiratory, and gastrointestinal infections (Table 5). Upper respiratory infections were the most common in the fifth wave (74.3%) and the least in the first wave (43.8%) ($p < 0.001$). Rhinitis and laryngitis were reported the most frequently. Lower respiratory infections were diagnosed based on clinical presentation and LU, chest X-ray, and HRCT. Lung imaging data from the children during the first five waves of the pandemic is shown in Table 6. It was the most common in the first wave (50%) and least common in the fifth wave (16.4%) ($p < 0.001$), whereas gastroenterocolitis was the most frequent in the fifth wave (24.4%) and the least in the first wave (8.9%). Significant differences were observed between the five waves in

the frequency of neurological diagnoses, especially between the second (0.6%) and fourth (16.6%) waves ($p < 0.001$).

Table 5. Final diagnoses during the first five waves of the pandemic.

	First Wave $n = 134$	Second Wave $n = 212$	Third Wave $n = 247$	Fourth Wave $n = 694$	Fifth Wave $n = 57$	p-Value
Upper respiratory tract infection	49 43.8%	99 56.9%	95 49.0%	277 54.6%	304 73.4%	<0.001
Lower respiratory tract infection	56 50.0%	53 30.5%	63 32.5%	162 32.0%	68 16.4%	<0.001
Gastroenterocolitis	10 8.9%	26 15.1%	32 16.5%	68 13.4%	101 24.4%	<0.001
Neurological diagnoses	5 4.5%	1 0.6%	16 8.2%	84 16.6%	41 9.9%	<0.001
Other	14 12.5%	33 19.1%	41 21.1%	103 20.3%	61 14.7%	0.07

n, number of diagnoses. Data are presented as *n* (%); *p*-value for chi-squared test.

Table 6. Lung imaging in COVID-19 pediatric patients hospitalized during the first five waves of the pandemic.

	First Wave $n = 112$	Second Wave $n = 175$	Third Wave $n = 195$	Fourth Wave $n = 511$	Fifth Wave $n = 414$
Chest X-ray, *n*	52	33	33	265	71
Positive X-ray, *n (%)*	24 (46)	25 (76)	33 (100)	149 (56)	51 (72)
Lung ultrasound, *n*	7	37	42	256	212
Positive lung ultrasound, *n (%)*	1 (14)	28 (76)	37 (88)	134 (52)	54 (18)
HRCT, *n*	0	0	2	11	0
Positive HRCT, *n* (%)	0	0	2 (100)	11 (100)	0

4. Discussion

To the best of our knowledge, this is the largest single-center study of children hospitalized due to COVID-19 and the first one comparing clinical presentations in children during the first five waves of the pandemic. Although children are considered to be less affected [12,18,19,49–51], 1407 were hospitalized between 23 March 2020 and 30 April 2022. This might have been due to the higher prevalence of SARS-CoV-2 in our local community and the central organization of hospital care in our region. The first wave of the pandemic was very mild in Poland because of the strict lockdown in the spring of 2020, which means that the relatively high number of hospitalized children in the first wave was the result of mandatory hospitalization for every infected SARS-CoV-2 patient [32] (Figure 1).

4.1. Demographic Characteristics

The demographic characteristics of the patients were similar in all five waves. There were no significant differences in sex, but there was a slight male predominance, as in other studies [15,16,20,50,52–54].

The ages of our patients were of particular interest. The median age in the first wave (95.8 months) was higher compared to the others (14.6–23 months). Similarly, infants aged zero to six months represented 26–29% of patients from the second to fifth waves. Other authors have reported the prevalence of both younger [2,15–17,54] and older children [8]. For example, Turan et al. [16] revealed the prevalence of younger children in the second wave compared to the first. It should be noted that, to the best of our knowledge, there has not been such a large study of the prevalence of children with COVID-19 at such a young

age. This can be explained by outbreaks of COVID-19 in large neonatal departments and the referral to our department of children at risk of a severe course of COVID-19. The Polish expert group recommendations also indicate the necessity of hospitalizing the youngest children [33]. It is noteworthy that our study included only hospitalized children.

4.2. Clinical Presentation

Though SARS-CoV-2 infection was common in children, the course of the disease was usually milder than for adults [12,18,19,49–51]. In our department, severe courses of the disease were rare, and there were no significant differences in severity over the five waves, although we did observe increased hospitalizations in the fourth and fifth waves. Similar observations regarding increasing numbers of hospitalization for the delta and omicron variants were reported by Marks et al. and Shi et al. [21–23]. However, we found significant differences in their clinical presentations. Similar observations have been reported by other authors [9,13,14,24–28,33,50].

The basic differences in the clinical presentation were the frequency of respiratory symptoms (rhinitis, cough, dyspnea, auscultatory changes, and lower respiratory infection), which increased from the second to the fourth waves. In contrast, gastrointestinal symptoms (vomiting and diarrhea) were the most common in the second wave. Other authors have reported fever and cough as the most frequent early symptoms [9–12]. During the predominance of the delta and omicron variants, upper respiratory tract symptoms (rhinitis and sore throat) were more common [29].

Anosmia and ageusia, the most significant symptoms of COVID-19, were very rare in the children: Fewer than 4% of the patients in our study, which differed significantly from previous reports. Most authors have emphasized that anosmia and ageusia caused by the omicron variant appeared much less often in the fifth wave [29,55–57]. This might have been caused by the specific nature of our cohort—only hospitalized children, who showed a significant decrease in age from wave to wave (Table 1). In the fifth wave, the median age was 14.6 months. This was a special group of patients who might require hospitalization for dehydration resulting from the refusal to take fluids due to smell and taste disorders. In such cases, medical help was sought, as feeding the youngest children proved difficult. In older children and adults, smell and taste disorders did not usually require hospitalization. It is noteworthy that the results were also affected by the team's increasing experience in COVID-19 diagnosis in the youngest group of patients, who were unable to verbalize their ailments. It is also worth emphasizing that some authors have reported the frequency of smell disorders in the fifth wave of the pandemic as 12% and taste as 23%, which was more frequent than in our cohort (13% in both cases) [58].

Regarding the final diagnoses of the hospitalized COVID-19 pediatric patients, the number of children with upper respiratory or gastroenterological symptoms was the highest in the fifth wave, while that of lower respiratory infection was most common in the first wave. Interestingly, Pokorska-Śpiewak et al. [12] reported in their study that pneumonia was more common in the second than in the first wave, but this can be explained by lower testing for SARS-CoV-2 infection of asymptomatic or mildly symptomatic children in our region during the first wave. We observed more upper than lower respiratory infections and shorter lengths of stay in hospital in the fifth wave. A lot of publications support our study's finding of a milder course for the omicron-dominated fifth wave in both adults and children [59–62]. Marks and Shi reported that the proportions of hospitalized children requiring PICU or intensive mechanical ventilation were similar in the first four waves but lower in the fifth [21–23]. Nevertheless, although most of the patients who contracted the SARS-CoV-2 omicron variant exhibited milder clinical features, severe clinical features, including mortality, were encountered among individuals who were not vaccinated [63].

In our cohort, more neurological symptoms occurred in the fourth wave. Similarly, in London, Molteni compared the disease course during the alpha and delta variant predomi-

nance and found more neurological symptoms (headaches, dizziness, chills, anosmia, and ageusia) during the delta variant period [19].

Antoon et al., who analyzed only serious neurological complications and those of clear significance (seizures, strokes, and encephalopathy), also reported that the most common neurological diagnoses occurred in the delta variant period (37.8%), while during the alpha and omicron periods, they were 5.6% and 5.1%, respectively. They also reported 42.7% of cases from the wild-type variant, otherwise than in our cohort [64]. The majority of our patients (69%) had no history of neurological diseases, and required special attention only when neurological or psychiatric disorders were a symptom of COVID-19. Such a possibility was pointed out by the CoroNerve Study Group in the U.K. [65], but this needs further investigation.

The differences in the course of COVID-19 between the five waves indicate the probable influence of different variants of SARS-CoV-2 on disease presentation. Until the second wave (October 2020 to January 2021), variants were not reported in Poland and SARS-CoV-2 sequencing was only performed occasionally. In the third wave (February to May 2021), the alpha (B.1.1.7) variant predominated and was reported to be associated with increased transmissibility (i.e., more efficient and rapid transmission). In January 2021, U.K. scientists reported evidence that suggested that the B.1.1.7 variant may be associated with an increased risk of death, but early reports found no evidence to suggest any effect on the severity of the disease [66]. In other countries, after the alpha variant announcement in December 2020, there were reports of increased admissions to hospital and more serious illnesses in children, indicating that the B.1.1.7. variant was more pathogenically infectious within this group [24]. Nevertheless, we found no evidence of more severe disease in children during the third wave, and we found that the B.1.1.7 variant did not result in an appreciably different clinical course than the original strain. The fourth wave was dominated by the B.1.617.2 delta variant, which was reported to have increased transmissibility. Many more patients were hospitalized and we observed more severe cases of COVID-19, but these were statistically insignificant. In the fifth wave, omicron (B.1.1.529, BA.1, BA.1.1, BA.2, BA.3, BA.4, and BA.5 lineages) dominated. The CDC announced that it caused a milder disease, although some people experienced a severe course, required hospitalization, and could have died from infection [67]. In this wave, we hospitalized 414 children and observed the shortest hospital stay.

In this study, the Bacillus Calmette–Guérin (BCG) vaccination was also considered to be a factor that influenced COVID-19 severity, because it was hypothesized that countries without widespread tuberculosis prevention policies had a higher percentage of severe cases (Italy, France, and Spain) than countries that adopted long-term widespread prevention (Japan, Denmark, and Korea). In Poland, antituberculosis BCG vaccination was obligatory, so in our pediatric study groups, over 95% of patients had been vaccinated. The lack of BCG vaccination was found in 2–4% of hospitalized children in different waves. We did not observe statistically significant differences in the number of hospitalized BCG-vaccinated and unvaccinated patients. However, various publications have described the results of the first association between BCG vaccination and COVID-19 cases, but these have concerned only adults [68,69].

Our study confirmed that the children had a much milder course of the virus and richer symptoms of COVID-19 compared to adults in all waves. The same has been reported in other studies [12,18,19,49–51].

4.3. Laboratory Findings

Only a few authors have compared the COVID-19 course in children between different waves of the pandemic. Most of them did not consider laboratory findings, while Murugan et al. did not find any significant differences in laboratory results (hemoglobin, total platelet count, creatinine, Alt, prothrombin time, partial thromboplastin time, D-dimer, and C-reactive protein) [9,10,13–15,24–26,70,71]. In our study, we found statistically significant

differences in the first five waves of the pandemic in terms of CRP, blood platelets, and lactate dehydrogenase.

Our study has several limitations. During the first and second waves, primary care for COVID-19 patients was limited, so they were often referred to hospital. The Polish Ministry of Health's recommendations about the rules for COVID-19 isolation and hospitalization changed in the subsequent waves, and this could have influenced the admission criteria and the length of hospitalization. Our experience with pediatric COVID-19 also expanded over the subsequent waves, which could also have influenced hospital admissions and the length of stay.

To the best of our knowledge, this is the first such large single-center study comparing the differences between the clinical course of pediatric COVID-19 in the first five waves of the pandemic.

5. Conclusions

Our findings confirmed that a life-threatening course of COVID-19 in children was relatively rare. However, children with pneumonia, dehydration from fever, gastrointestinal symptoms, and loss of smell and taste, as well as those with neurological symptoms, represented most of the patients requiring hospitalization.

The absolute number of hospitalizations was significantly higher in the fourth and fifth waves than in the first three waves. The clinical course of the disease changed between March 2020 and April 2022 due to the predominance of different SARS-CoV-2 variants.

Author Contributions: Conceptualization, L.S. and P.K.; methodology, L.S. and P.K.; investigation, L.S., P.K., A.K., I.M., J.S. (Justyna Stala), J.S. (Justyna Szebla), M.J., and K.G.; data interpretation, L.S. and P.K.; writing—original draft preparation, L.S., P.K., and A.K.; supervision: L.S. and P.K. All authors have read and agreed to the published version of the manuscript.

Funding: This research received no external funding.

Institutional Review Board Statement: This study was conducted in accordance with the Declaration of Helsinki, and approved by the Institutional Ethics Committees. Name of the Ethics Committee: Regional Medical Chamber in Krakow, No. OIL/KBL/18/2020.

Informed Consent Statement: Not applicable.

Data Availability Statement: The datasets used and analyzed during the current study are available from the corresponding author upon reasonable request.

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

References

1. Coronavirus Disease (COVID-19) Pandemic. Available online: https://www.who.int/emergencies/diseases/novel-coronavirus-2019 (accessed on 21 July 2022).
2. Lu, X.; Zhang, L.; Du, H.; Zhang, J.; Li, Y.; Qu, J.; Zhang, W.; Wang, Y.; Bao, S.; Li, Y.; et al. SARS-CoV-2 Infection in Children. *N. Engl. J. Med.* **2020**, *382*, 1663–1665. [CrossRef] [PubMed]
3. Parri, N.; Lenge, M.; Buonsenso, D. Children with COVID-19 in Pediatric Emergency Departments in Italy. *N. Engl. J. Med.* **2020**, *383*, 187–190. [CrossRef] [PubMed]
4. Children and COVID-19: State-Level Data Report. Available online: https://www.aap.org/en/pages/2019-novel-coronavirus-covid-19-infections/children-and-covid-19-state-level-data-report/ (accessed on 21 July 2022).
5. Demographic Trends of COVID-19 Cases and Deaths in the US Reported to CDC. Available online: https://covid.cdc.gov/covid-data-tracker/?CDC_AA_refVal=https%253A%252F%252Fwww.cdc.gov%252Fcoronavirus%252F2019-ncov%252Fcases-updates%252Fcases-in-us.html#demographics (accessed on 21 July 2022).
6. Data on the 14-Day Age-Specific Notification Rate of New COVID-19 Cases. Available online: https://www.ecdc.europa.eu/en/publications-data/covid-19-data-14-day-age-notification-rate-new-cases (accessed on 20 May 2022).
7. Assaker, R.; Colas, A.E.; Julien-Marsollier, F.; Bruneau, B.; Marsac, L.; Greff, B.; Tri, N.; Fait, C.; Brasher, C.; Dahmani, S. Presenting symptoms of COVID-19 in children: A meta-analysis of published studies. *Br. J. Anaesth.* **2020**, *125*, e330–e332. [CrossRef] [PubMed]

8. Castagnoli, R.; Votto, M.; Licari, A.; Brambilla, I.; Bruno, R.; Perlini, S.; Rovida, F.; Baldanti, F.; Marseglia, G.L. Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) Infection in Children and Adolescents: A Systematic Review. *JAMA Pediatr.* **2020**, *174*, 882–889. [CrossRef] [PubMed]
9. Zimmermann, P.; Curtis, N. Coronavirus Infections in Children Including COVID-19: An Overview of the Epidemiology, Clinical Features, Diagnosis, Treatment and Prevention Options in Children. *Pediatr. Infect. Dis. J.* **2020**, *39*, 355–368. [CrossRef]
10. Oliveira, E.A.; Simões, E.; Silva, A.C.; Oliveira, M.C.L.; Colosimo, E.A.; Mak, R.H.; Vasconcelos, M.A.; Miranda, D.M.; Martelli, D.B.; Silva, L.R.; et al. Comparison of the First and Second Waves of the Coronavirus Disease 2019 Pandemic in Children and Adolescents in a Middle-Income Country: Clinical Impact Associated with Severe Acute Respiratory Syndrome Coronavirus 2 Gamma Lineage. *J. Pediatr.* **2022**, *244*, 178–185.e3. [CrossRef]
11. Krishnamurthy, S.; Kar, S.S.; Dhodapkar, R.; Parameswaran, N. Comparison of COVID-19 Infection in Children During the First and Second Wave. *Indian J. Pediatr.* **2022**, *19*, 1–3. [CrossRef]
12. Pokorska-Śpiewak, M.; Talarek, E.; Mania, A.; Pawłowska, M.; Popielska, J.; Zawadka, K.; Figlerowicz, M.; Mazur-Melewska, K.; Faltin, K.; Ciechanowski, P.; et al. Clinical and Epidemiological Characteristics of 1283 Pediatric Patients with Coronavirus Disease 2019 during the First and Second Waves of the Pandemic—Results of the Pediatric Part of a Multicenter Polish Register SARSTer. *J. Clin. Med.* **2021**, *10*, 5098. [CrossRef]
13. Swann, O.V.; Holden, K.A.; Turtle, L.; Pollock, L.; Fairfield, C.J.; Drake, T.M.; Seth, S.; Egan, C.; Hardwick, H.E.; Halpin, S.; et al. Clinical characteristics of children and young people admitted to hospital with COVID-19 in United Kingdom: Prospective multicentre observational cohort study. *BMJ* **2020**, *370*, m3249. [CrossRef]
14. Garazzino, S.; Lo Vecchio, A.; Pierantoni, L.; Calò Carducci, F.I.; Marchetti, F.; Meini, A.; Castagnola, E.; Vergine, G.; Dona, D.; Bosis, S.; et al. Epidemiology, Clinical Features and Prognostic Factors of Pediatric SARS-CoV-2 Infection: Results from an Italian Multicenter Study. *Front. Pediatr.* **2021**, *9*, 649358. [CrossRef]
15. Badal, S.; Thapa Bajgain, K.; Badal, S.; Thapa, R.; Bajgain, B.B.; Santana, M.J. Prevalence, clinical characteristics, and outcomes of pediatric COVID-19: A systematic review and meta-analysis. *J. Clin. Virol. Off. Publ. Pan. Am. Soc. Clin. Virol.* **2021**, *135*, 104715. [CrossRef] [PubMed]
16. Turan, C.; Basa, E.G.; Elitez, D.; Yılmaz, Ö.; Gumus, E.; Anıl, M. The Comparison of Children Who Were Diagnosed with COVID-19 in the First and the Second Waves of the SARS-CoV-2 Pandemic. *Turkish Arch. Pediatr.* **2021**, *56*, 596–601. [CrossRef] [PubMed]
17. Chua, G.T.; Wong, J.S.C.; Lam, I.; Ho, P.P.K.; Chan, W.H.; Yau, F.Y.S.; Duque, J.S.R.; Ho, A.C.C.; Siu, K.K.; Cheung, T.W.Y.; et al. Clinical Characteristics and Transmission of COVID-19 in Children and Youths During 3 Waves of Outbreaks in Hong Kong. *JAMA Netw. Open* **2021**, *4*, e218824. [CrossRef] [PubMed]
18. Flisiak, R.; Rzymski, P.; Zarębska-Michaluk, D.; Rogalska, M.; Rorat, M.; Czupryna, P.; Lorenc, B.; Ciechanowski, P.; Kozielewicz, D.; Piekarska, A.; et al. Demographic and Clinical Overview of Hospitalized COVID-19 Patients during the First 17 Months of the Pandemic in Poland. *J. Clin. Med.* **2021**, *11*, 117. [CrossRef]
19. Molteni, E.; Sudre, C.H.; Canas, L.D.S.; Bhopal, S.S.; Hughes, R.C.; Chen, L.; Deng, J.; Murray, B.; Kerfoot, E.; Antonelli, M.; et al. Illness Characteristics of COVID-19 in Children Infected with the SARS-CoV-2 Delta Variant. *Children* **2022**, *9*, 652. [CrossRef]
20. Rovida, F.; Giardina, F.; Ferrari, G.; Paolucci, S.; Piralla, A.; Baldanti, F. SARS-CoV-2 infections in pediatric patients: A comparison of three pandemic waves. *Pediatric Allergy Immunol. Off. Publ. Eur. Soc. Pediatr. Allergy Immunol.* **2022**, *33* (Suppl. S27), 93–95. [CrossRef]
21. Marks, K.J.; Whitaker, M.; Anglin, O.; Milucky, J.; Patel, K.; Pham, H.; Chai, S.J.; Kirley, P.D.; Armistead, I.; McLafferty, S.; et al. COVID-NET Surveillance Team. Hospitalizations of Children and Adolescents with Laboratory-Confirmed COVID-19—COVID-NET, 14 States, July 2021–January 2022. *MMWR Morb. Mortal. Wkly. Rep.* **2022**, *71*, 271–278. [CrossRef]
22. Marks, K.J.; Whitaker, M.; Agathis, N.T.; Anglin, O.; Milucky, J.; Patel, K.; Pham, H.; Kirley, P.D.; Kawasaki, B.; Meek, J.; et al. COVID-NET Surveillance Team. Hospitalization of Infants and Children Aged 0–4 Years with Laboratory-Confirmed COVID-19—COVID-NET, 14 States, March 2020–February 2022. *MMWR Morb. Mortal. Wkly. Rep.* **2022**, *71*, 429–436. [CrossRef]
23. Shi, D.S.; Whitaker, M.; Marks, K.J.; Anglin, O.; Milucky, J.; Patel, K.; Pham, H.; Chai, S.J.; Kawasaki, B.; Meek, J.; et al. COVID-NET Surveillance Team. Hospitalizations of Children Aged 5–11 Years with Laboratory-Confirmed COVID-19—COVID-NET, 14 States, March 2020–February 2022. *MMWR Morb. Mortal. Wkly. Rep.* **2022**, *71*, 574–581. [CrossRef]
24. Brookman, S.; Cook, J.; Zucherman, M.; Broughton, S.; Harman, K.; Gupta, A. Effect of the new SARS-CoV-2 variant B.1.1.7 on children and young people. *Lancet Child Adolesc. Health* **2021**, *5*, e9–e10. [CrossRef]
25. Murugan, P.T.; Ghosh, U.; Rajan, R.J.; Punnen, A.; Chandran, J.; Das Adhikari, D.; Mathew, L.G.; Rose, W. Spectrum of COVID-19 Disease in Children: A Retrospective Analysis Comparing Wave 1 and Wave 2 from a Tertiary Hospital in South India. *Indian J. Pediatr.* **2022**, *25*, 1–7.
26. Alteri, C.; Scutari, R.; Costabile, V.; Colagrossi, L.; Yu La Rosa, K.; Agolini, E.; Lanari, V.; Chiurciu, S.; Romani, L.; Markowich, A.H.; et al. Epidemiological characterization of SARS-CoV-2 variants in children over the four COVID-19 waves and correlation with clinical presentation. *Sci. Rep.* **2022**, *12*, 10194. [CrossRef] [PubMed]
27. Krajcar, N.; Stemberger Marić, L.; Surina, A.; Kurečić Filipović, S.; Trkulja, V.; Roglić, S.; Tesović, G. Epidemiological and clinical features of Croatian children and adolescents with a PCR-confirmed coronavirus disease 2019: Differences between the first and second epidemic wave. *Croat. Med. J.* **2020**, *61*, 491–500. [CrossRef] [PubMed]

28. Yock-Corrales, A.; Gomez-Vargas, J.; Ulloa-Gutierrez, R.; Brizuela, M.; Del Aguila, O.; Kozicki, V.; Lenzi, J.; Buonsenso, D. Clinical Outcomes of Pediatric COVID-19 During Two Waves of Different Variants Circulation in Latin America. *Indian J. Pediatr.* **2022**, *89*, 727. [CrossRef] [PubMed]
29. Menni, C.; Valdes, A.M.; Polidori, L.; Antonelli, M.; Penamakuri, S.; Nogal, A.; Louca, P.; May, A.; Figueiredo, J.C.; Hu, C.; et al. Symptom prevalence, duration, and risk of hospital admission in individuals infected with SARS-CoV-2 during periods of omicron and delta variant dominance: A prospective observational study from the ZOE COVID Study. *Lancet* **2022**, *399*, 1618–1624. [CrossRef]
30. WHO Recommendations for National SARS-CoV-2 Testing Strategies and Diagnostic Capacities. Available online: https://www.who.int/publications/i/item/WHO-2019-nCoV-lab-testing-2021.1-eng (accessed on 24 August 2022).
31. Polish National Institute of Public Health Recommendations on SARS-Cov2 Laboratory Diagnostics. Available online: https://www.pzh.gov.pl/koronawirus-sars-cov-2/wytyczne-i-rekomendacje/ (accessed on 24 August 2022).
32. Regulation of the Polish Minister of Health from 16 March 2020. Available online: https://legislacja.rcl.gov.pl/projekt/12331301/katalog/12669385#12669385 (accessed on 24 August 2022).
33. Marczyńska, M.; Figlerowicz, M.; Kalicki, B.; Kuchar, E.; Majda-Stanisławska, E.; Pawłowska, M.; Sulik, A.; Sybilski, A.; Szenborn, L.; Wysocki, J.; et al. Management of a Child with COVID-19 Recommendations for Pediatricians and Family Medicine Physicians in Primary Healthcare and Hospital Settings. Available online: https://ptp.edu.pl/dokumenty/covid/post_z_dzieckiem_covid-19.pdf (accessed on 21 July 2022).
34. EMA Assesment Report. Dexamethasone in Hospitalised Patients with COVID-19. Available online: https://www.ema.europa.eu/en/documents/other/dexamethasone-covid19-article-53-procedure-assessment-report_en.pdf (accessed on 24 August 2022).
35. EMA Summary of Product Characteristics Veklury 100 mg. Available online: https://www.ema.europa.eu/en/documents/other/veklury-product-information-approved-chmp-25-june-2020-pending-endorsement-european-commission_en.pdf (accessed on 24 August 2022).
36. CHKD Treatment Guideline for COVID-19 in Children. Available online: https://www.chkd.org/uploadedFiles/Documents/COVID-19/CHKD%20COVID%2019%20treatment%20guideline.pdf (accessed on 24 August 2022).
37. COVID-19 Drug Interactions. University of Liverpool. Available online: https://www.covid19-druginteractions.org/ (accessed on 24 August 2022).
38. Chiotos, K.; Hayes, M.; Kimberlin, D.W.; Jones, S.B.; James, S.H.; Pinninti, S.G.; Yarbrough, A.; Abzug, M.J.; MacBrayne, C.E.; Soma, V.L.; et al. Multicenter Initial Guidance on Use of Antivirals for Children with Coronavirus Disease 2019/Severe Acute Respiratory Syndrome Coronavirus 2. *J. Pediatric Infect. Dis. Soc.* **2020**, *9*, 701–715. [CrossRef] [PubMed]
39. COVID-19: Management in Children. Uptodate. Available online: https://www.uptodate.com/contents/covid-19-management-in-children (accessed on 24 August 2022).
40. Russel, K.F.; Liang, Y.; O'Gorman, K.; Johnson, D.W.; Klassen, T.P. Glucocorticosteroids for croup. *Cochrane Database Syst. Rev.* **2011**, *1*, CD001955.
41. Petrocheilou, A.; Tanou, K.; Kalampouka, E.; Malakasioti, G.; Giannios, C.; Kaditis, A.G. Viral croup: Diagnosis and a treatment algorithm. *Pediatric Pulmonol.* **2014**, *49*, 421–429. [CrossRef]
42. Fact Sheet for Healthcare Providers Emergency Use Authorization (EUA) of Veklury®(Remdesivir) for the Treatment of Coronavirus Disease 2019 (COVID-19) in Pediatric Patients Weighing 3.5 kg to Less Than 40 kg or Pediatric Patients Less Than 12 Years of Age Weighing at Least 3.5 kg, with Positive Results of Direct SARS-CoV-2 Viral Testing Who Are: Hospitalized, or not Hospitalized and Have Mild-to-Moderate COVID-19, and Are at High Risk for Progression to Severe COVID-19, Including Hospitalization or death. Available online: https://www.fda.gov/media/137566/download (accessed on 24 August 2022).
43. Fact Sheet for Healthcare Providers Emergency Use Authorization (EUA) of Baricitinib. Available online: https://www.fda.gov/media/143823/download (accessed on 24 August 2022).
44. Pereda, M.A.; Chavez, M.A.; Hooper-Miele, C.C.; Gilman, R.H.; Steinhoff, M.C.; Ellington, L.E.; Gross, M.; Price, C.; Tielsch, J.M.; Checkley, W. Lung ultrasound for the diagnosis of pneumonia in children: A meta-analysis. *Pediatrics* **2015**, *135*, 714–722. [CrossRef]
45. Palabiyik, F.; Kokurcan, S.O.; Hatipoglu, N.; Cebeci, S.O.; Inci, E. Imaging of COVID-19 pneumonia in children. *Br. J. Radiol.* **2020**, *93*, 20200647. [CrossRef]
46. Peixoto, A.O.; Costa, R.M.; Uzun, R.; Fraga, A.M.A.; Ribeiro, J.D.; Marson, F.A.L. Applicability of lung ultrasound in COVID-19 diagnosis and evaluation of the disease progression: A systematic review. *Pulmonology* **2021**, *27*, 529–562. [CrossRef] [PubMed]
47. Daily COVID-19 Cases in the Malopolska Region. Available online: https://koronawirusunas.pl/wojewodztwo-malopolskie (accessed on 21 July 2022).
48. The Proportion of Total Number of COVID-19 Sequences OVER time in Poland. Available online: https://covariants.org/ (accessed on 21 July 2022).
49. Cusenza, F.; Davino, G.; D'Alvano, T.; Argentiero, A.; Fainardi, V.; Pisi, G.; Principi, N.; Esposito, S. Silence of the Lambs: The Immunological and Molecular Mechanisms of COVID-19 in Children in Comparison with Adults. *Microorganisms* **2021**, *7*, 330. [CrossRef] [PubMed]
50. Swann, O.V.; Pollock, L.; Holden, K.A.; Munro, A.P.S.; Bennett, A.; Williams, T.C.; Turtle, L.; Fairfield, C.J.; Drake, T.M.; Faust, S.N.; et al. Comparison of UK paediatric SARS-CoV-2 admissions across the first and second pandemic waves. *Pediatr. Res.* **2022**. *Online ahead of print*. [CrossRef] [PubMed]

51. O'Driscoll, M.; Ribeiro Dos Santos, G.; Wang, L.; Cummings, D.A.T.; Azman, A.S.; Paireau, J.; Fontanet, A.; Cauchemez, S.; Salje, H. Age-specific mortality and immunity patterns of SARS-CoV-2. *Nature* **2021**, *590*, 140–145. [CrossRef] [PubMed]
52. Graff, K.; Smith, C.; Silveira, L.; Jung, S.; Curran-Hays, S.; Jarjour, J.; Carpenter, L.; Pickard, K.; Matiucci, M.; Fresia, J.; et al. Risk Factors for Severe COVID-19 in Children. *Pediatric Infect. Dis. J.* **2021**, *40*, e137–e145. [CrossRef] [PubMed]
53. Götzinger, F.; Santiago-García, B.; Noguera-Julián, A.; Lanaspa, M.; Lancella, L.; Calò Carducci, F.I.; Gabrovska, N.; Velizarova, S.; Prunk, P.; Osterman, V.; et al. COVID-19 in children and adolescents in Europe: A multinational, multicentre cohort study. *Lancet Child Adolesc. Health* **2020**, *4*, 653–661. [CrossRef]
54. Mania, A.; Mazur-Melewska, K.; Lubarski, K.; Kuczma-Napierała, J.; Mazurek, J.; Jończyk-Potoczna, K.; Służewski, W.; Figlerowicz, M. Wide spectrum of clinical picture of COVID-19 in children—From mild to severe disease. *J. Infect. Public Health* **2021**, *14*, 374–379. [CrossRef]
55. Tseng, F.H.; Yeh, S.H.; Basiago, K.; Miyares, W.; Zangwill, K.M. Is Acute Solid Food Aversion a Proxy for COVID-19-Related Olfactory and Gustatory Dysfunction? *Pediatrics* **2021**, *15*, e2021052534. [CrossRef]
56. Coelho, D.H.; Reiter, E.R.; French, E.; Costanzo, R.M. Decreasing Incidence of Chemosensory Changes by COVID-19 Variant. *Otolaryngol. Head Neck Surg.* **2022**, *3*, 1945998221097656. [CrossRef]
57. Boscolo-Rizzo, P.; Tirelli, G.; Meloni, P.; Hopkins, C.; Madeddu, G.; De Vito, A.; Gardenal, N.; Valentinotti, R.; Tofanelli, M.; Borsetto, D.; et al. Coronavirus disease 2019 (COVID-19)-related smell and taste impairment with widespread diffusion of severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2) Omicron variant. *Int. Forum Allergy Rhinol.* **2022**. [CrossRef]
58. Brandal, L.T.; MacDonald, E.; Veneti, L.; Ravlo, T.; Lange, H.; Naseer, U.; Feruglio, S.; Bragstad, K.; Hungnes, O.; Ødeskaug, L.E.; et al. Outbreak caused by the SARS-CoV-2 Omicron variant in Norway, November to December 2021. *Eurosurveillance* **2021**, *26*, 2101147. [CrossRef] [PubMed]
59. Butt, A.A.; Dargham, S.R.; Loka, S.; Shaik, R.M.; Chemaitelly, H.; Tang, P.; Hasan, M.R.; Coyle, P.V.; Yassine, H.M.; Al-Khatib, H.A.; et al. COVID-19 Disease Severity in Children Infected with the Omicron Variant. *Clin. Infect. Dis.* **2022**, *11*, ciac275.
60. Liu, X.; Chen, M.; Zhou, Z.; Chen, D.; Mo, J.; Liu, J. Epidemiological characteristics of 17 imported patients infected with SARS-CoV-2 Omicron variant. *Zhong Nan Da Xue Xue Bao Yi Xue Ban* **2022**, *47*, 344–351. [PubMed]
61. Wang, X.L.; Zhai, J.; Zou, Y.X. Clinical characteristics and vaccination status of SARS-CoV-2 Omicron variant infected children. *Zhonghua Er Ke Za Zhi* **2022**, *60*, 671–675.
62. Petersen, M.S.; Kongsstovu, S.; Eliasen, E.H.; Larsen, S.; Hansen, J.L.; Vest, N.; Dahl, M.M.; Christiansen, D.H.; Møller, L.F.; Kristiansen, M.F. Clinical characteristics of the Omicron variant—Results from a Nationwide Symptoms Survey in the Faroe Islands. *Int. J. Infect. Dis.* **2022**, *122*, 636–643. [CrossRef]
63. Sohn, Y.J.; Shin, P.J.; Oh, W.S.; Kim, E.; Kim, Y.; Kim, Y.K. Clinical Characteristics of Patients Who Contracted the SARS-CoV-2 Omicron Variant from an Outbreak in a Single Hospital. *Yonsei Med. J.* **2022**, *63*, 790–793. [CrossRef]
64. Antoon, J.W.; Hall, M.; Howard, L.M.; Herndon, A.; Freundlich, K.L.; Grijalva, C.G.; Williams, D.J. COVID-19 and Acute Neurologic Complications in Children. *Pediatrics* **2022**, *150*, e2022058167. [CrossRef]
65. Ray, S.T.J.; Abdel-Mannan, O.; Sa, M.; Fuller, C.; Wood, G.K.; Pysden, K.; Yoong, M.; McCullagh, H.; Scott, D.; McMahon, M.; et al. Neurological manifestations of SARS-CoV-2 infection in hospitalised children and adolescents in the UK: A prospective national cohort study. *Lancet Child Adolesc. Health* **2021**, *5*, 631–641. [CrossRef]
66. SARS-CoV-2 Variant Classifications and Definitions. Available online: https://www.cdc.gov/coronavirus/2019-ncov/variants/variant-classifications.html (accessed on 21 July 2022).
67. Omicron Variant: What You Need to Know. Available online: https://www.cdc.gov/coronavirus/2019-ncov/variants/omicron-variant.html (accessed on 21 July 2022).
68. Czajka, H.; Zapolnik, P.; Krzych, Ł.; Kmiecik, W.; Stopyra, L.; Nowakowska, A.; Jackowska, T.; Darmochwał-Kolarz, D.; Szymański, H.; Radziewicz-Winnicki, I.; et al. A Multi-Center, Randomised, Double-Blind, Placebo-Controlled Phase III Clinical Trial Evaluating the Impact of BCG Re-Vaccination on the Incidence and Severity of SARS-CoV-2 Infections among Symptomatic Healthcare Professionals during the COVID-19 Pandemic in Poland-First Results. *Vaccines* **2022**, *10*, 314.
69. Li, Y.; Zhao, S.; Zhuang, Z.; Cao, P.; Yang, L.; He, D. The Correlation between BCG Immunization Coverage and the Severity of COVID-19. Available online: https://ssrn.com/abstract=3568954 (accessed on 21 July 2022).
70. Gaythorpe, K.A.M.; Bhatia, S.; Mangal, T.; Unwin, H.J.T.; Imai, N.; Cuomo-Dannenburg, G.; Walters, C.E.; Jauneikaite, E.; Bayley, H.; Kont, M.D.; et al. Publisher Correction: Children's role in the COVID-19 pandemic: A systematic review of early surveillance data on susceptibility, severity, and transmissibility. *Sci. Rep.* **2021**, *11*, 18814. [CrossRef]
71. Twohig, K.A.; Nyberg, T.; Zaidi, A.; Thelwall, S.; Sinnathamby, M.A.; Aliabadi, S.; Seaman, S.R.; Harris, R.J.; Hoper, R.; Lopez-Bernal, J.; et al. Hospital admission and emergency care attendance risk for SARS-CoV-2 delta (B.1.617.2) compared with alpha (B.1.1.7) variants of concern: A cohort study. *Lancet Infect. Dis.* **2022**, *22*, 35–42. [CrossRef]

6.2. Publikacia druga

Journal of
Clinical Medicine

MDPI

Article

The Age-Related Course of COVID-19 in Pediatric Patients—1405 Cases in a Single Center

Lidia Stopyra [1,2,*], Aleksandra Kowalik [3], Justyna Stala [1], Ida Majchrzak [1], Justyna Szebla [1], Mateusz Jakosz [1] and Przemko Kwinta [3]

[1] Department of Infectious Diseases and Pediatrics, Zeromski Specialist Hospital in Krakow, 30-931 Kraków, Poland
[2] Department of Pediatrics, Andrzej Frycz Modrzewski Krakow University, 30-705 Kraków, Poland
[3] Department of Pediatrics, Jagiellonian University Medical College, 30-663 Kraków, Poland
* Correspondence: lstopyra@zeromski-szpital.pl; Tel.: +48-126-229-513

Abstract: Since the beginning of the pandemic, many reports have pointed to age as the most important risk factor for severe COVID-19 in adults, but this relationship is less clear in children. Between March 2020 and April 2022, 1405 pediatric COVID-19 patients were included in our prospective study, which aimed to analyze the disease's characteristics in three age groups: infants, toddlers (1–5 years), and children (5–18 years). We observed male prevalence of the disease in infants and toddlers compared to female prevalence in children. Comorbidities appeared most often in children. In the first pandemic wave, the vast majority of pediatric patients were children, but later, the percentage of infant and toddler patients increased significantly. A total of 74% of hospitalized children were younger than five years. Upper respiratory tract symptoms were most common in infants and toddlers, and lower respiratory tract symptoms and gastroenterocolitis were more common in children. Neurological symptoms appeared similarly in all age groups. The activities of ALT, CK, and LDH were the most elevated in infants, along with D-dimers. The median length of hospitalization fluctuated between three and four days and was highest in infants. Severe courses were more common in adolescents.

Keywords: SARS-CoV-2; COVID-19; children; age; clinical presentation

Citation: Stopyra, L.; Kowalik, A.; Stala, J.; Majchrzak, I.; Szebla, J.; Jakosz, M.; Kwinta, P. The Age-Related Course of COVID-19 in Pediatric Patients—1405 Cases in a Single Center. *J. Clin. Med.* **2022**, *11*, 7347. https://doi.org/10.3390/jcm11247347

Academic Editor: Marlene Fischer

Received: 13 November 2022
Accepted: 7 December 2022
Published: 10 December 2022

1. Introduction

In December 2019, a cluster of severe, life-threatening cases of pneumonia was detected in the region of Wuhan in central China, and on 7 January 2020, the causative pathogen was identified as a novel RNA betacoronavirus. Because of its phylogenetic similarity to severe acute respiratory syndrome coronavirus (SARS-CoV), the new virus was named SARS-CoV-2 [1]. On 11 March 2020, the World Health Organization (WHO) announced the Coronavirus Disease 2019 (COVID-19) pandemic.

Many reports point to age as the most important risk factor for a severe course of COVID-19, and deaths in adults, while children were reported all over the world to present with an asymptomatic or mild course of the disease [2–7]. SARS-CoV-2-related death in children is rare. In the United States, as of 1 June 2022, there were >13 million cases of COVID-19 and 1533 COVID-19-associated deaths in children <18 years of age (<0.01%) reported to the CDC [8]. A small number of publications considered the problem of dependence between the course of COVID-19, the clinical presentation, the necessity for hospitalization, and age in pediatric patients. Their authors reported the prevalence in both young children and older children among hospitalized patients, meaning those with a more severe course of the disease [9–14]. Further investigation is necessary to understand the clinical presentation, laboratory findings, and indications for hospitalization, especially because of the changing COVID-19 course in pandemic waves caused by different SARS-CoV-2 variants [12,14–17].

This work aimed to analyze the COVID-19 characteristics of children in a single center, based on findings from 1405 patients aged 0 to 18 years that were hospitalized from 23 March 2020 to 30 April 2022. The analysis was conducted especially in terms of clinical presentation, laboratory findings, trends in pandemic waves, and outcomes in relation to age. Our observations may be useful for ongoing guidance for the evaluation, management, and prevention of COVID-19 for pediatric patients, depending on age.

2. Materials and Methods

On 23 March 2020, when the first children were admitted to the Department of Infectious Diseases and Pediatrics, this prospective study was started. The inclusion criteria were as follows: age 0–18 years, laboratory-confirmed COVID-19, and hospitalization. A total of 1405 children were included in this study. All of the children were symptomatic, and reinfections were included.

According to the World Health Organization (WHO) and the National Institute of Public Health recommendations [18,19], COVID-19 was diagnosed using a positive reverse transcription and real-time polymerase chain reaction (RT-PCR) and, since 30 October 2020, using the second-generation antigen tests based on a nasopharyngeal swab performed in certified laboratories. Several kits were used during the two years of the pandemic: (1) GeneFinder™ COVID-19 Plus RealAmp, Elitech, Biomedica, (2) Liferiver, Novel Coronavirus (2019-nCoV) Real Time Multiplex, (3) VIASURE CerTest, Biotec, (4) Maccura SARS-CoV-2 Fluorescent PCR, Maccura Biotechnology, (5) Homemade DIAGtest SARS-CoV-2 real time RT-PCR, and (6) Labsystems Diagnostics. In addition, we used the COVID-19 Real Time Multiplex RT-PCR and the second-generation Abbott Panbio-COVID-19 Ag Rapid Test Device (WHO laboratory 2020, AOTM).

The criteria for admission to the hospital were as per those for other pediatric diseases, e.g., dehydration, dyspnea, or seizures. According to the Polish Ministry of Health recommendations, hospitalization was compulsory for every patient with diagnosed SARS-CoV-2 infection up to September 2020 [20]. According to Polish expert group recommendations, hospital referrals were also required for children with congenital heart defects, neurologic diseases, genetic disorders, chronic renal diseases, mucoviscidosis, broncho-pulmonary dysplasia, immunodeficiency after organ transplantation, and diabetes mellitus. Newborns, infants, and children with obesity, especially those with a body mass index (BMI) > 30 kg/m^2, were also included [21].

Discharge criteria were two negative PCR tests taken within 24 h. After 2 September 2020, the only criterion was the condition of the patient.

Data were collected and reported by the physicians working in the department according to a standardized questionnaire for the case history and physical examination that were obligatory for every patient. The standard laboratory tests for COVID-19 patients were taken for every hospitalized child with diagnosed COVID-19.

The questionnaire included the following:

Demographic and epidemiological data: (age, sex, ethnicity, nasopharyngeal/oral swabs for SARS-CoV-2 PCR obtainment date, recent contact with known COVID-19 patients, background illnesses including heart disease, chronic lung disease, and/or asthma, developmental delay, diabetes, immune compromise, and malignancy).

Signs and symptoms: fever, cough, rhinitis, dyspnea, sore throat, weakness, diarrhea, abdominal pain, vomiting, headache, conjunctivitis, nausea, myalgia, rash, ageusia, anosmia, chest pain, irritability, seizures, and headache. Anosmia/ageusia are difficult to ascertain for infants and toddlers. In the study it was assumed that, if an infant or toddler with COVID-19 completely refused to eat for several consecutive days, and other reasons such as severe condition and stomatitis were excluded, the patient had anosmia/ageusia.

Disease outcome data: the length of hospitalization, the necessity of oxygen treatment, the necessity of intravenous dehydration, antiviral treatment, systemic steroid therapy, and PICU admission.

Laboratory data: complete blood count (CBC) parameters, C-reactive protein (CRP), alanine transaminase (ALT), lactate dehydrogenase (LDH), creatinine kinase (CK), ferritin, vitamin D3 level, prothrombin time, D-dimers, nasal swabs for other viral pathogens (co-infection), and imaging (i.e., lung ultrasound (LU), chest X-ray, and high-resolution computed tomography (HRCT)).

Final diagnoses: upper respiratory tract infection, lower respiratory tract infection, gastroenterocolitis, neurological diagnoses, and others.

Radiographic and USG pneumonia diagnoses were based on the interpretation by the treating physician. Lower respiratory infections were diagnosed based on clinical presentation and lung ultrasonography (LU), chest X-rays, and high-resolution computed tomography (HRCT). The most often administered examination, especially in the youngest children, was LU. The presence of focal, multifocal, and confluent B lines and pleural irregularities were the most common LU findings used to diagnose COVID-19 pneumonia. In chest X-ray examinations, bilateral and multifocal lesions were found most frequently, especially in the lower lobes. A pure ground-glass appearance was also typical of COVID-19 lower respiratory-related findings. Gastrointestinal infection was diagnosed based on clinical presentation (vomiting, diarrhea) and the exclusion of other etiologies such as rotaviruses, adenoviruses, and noroviruses.

To assess the COVID-19 characteristics depending on age, all 1405 hospitalized pediatric patients were assigned to three study groups: 567 infants (0–12 months), 470 toddlers (1–5 years), and 368 children (5–18 years).

The statistical analysis was performed using SPSS ver. 27 software (Armonk, NY, USA). Results were presented based on the parameters of descriptive statistics, including the mean values and standard deviations (SD) for the quantitative variables with a normal distribution or median values with the interquartile range for non-normally distributed data. Categorical variables were presented as numbers with percentages. Qualitative values were compared by the chi-square test. The Kruskal–Wallis test was used for the analysis of the continuous variables investigated in the study. In all cases of statistical significance, a pairwise comparison between the groups was performed using a post-hoc test. In all analyses, a p-value < 0.05 was considered statistically significant.

The study was performed in accordance with the ethical standards of the Declaration of Helsinki and its later amendments. It was approved by the Ethics Committee of the Regional Medical Chamber in Krakow No OIL/KBL/18/2020 on 10 March 2020.

3. Results

The age of the hospitalized children is presented in Figure 1. The high prevalence of infants younger than six months of age (26%) is noteworthy.

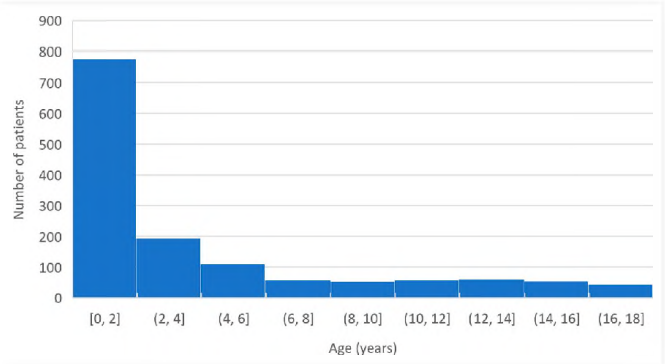


Figure 1. The age structure of the hospitalized children.

3.1. Study Groups

The demographic characteristic data are presented in Table 1.

Table 1. Demographic characteristics of hospitalized COVID-19 pediatric patients in the infant, toddler, and children groups.

	Infants (n = 567)	Toddlers (n = 470)	Children (n = 368)	p-Value
Male sex: n (%)	313 (55.3)	254 (54.2)	173 (47.5)	0.054
Patients with chronic diseases: n (%)	85 (15.2)	119 (25.4)	153 (42.3)	<0.001
Immunocompromised patients: n (%)	4 (0.7)	4 (0.9)	13 (3.6)	0.001
BCG unvaccinated patients: n (%)	23 (4.2)	12 (2.6)	5 (1.4)	0.047

BCG. Bacillus Calmette-Guerin.

The male sex was dominant in the groups of infants and toddlers, with the opposite finding for older children. However, the differences were not statistically significant. Only one child was South Asian; the rest (n = 1404) were Caucasian.

Immunocompromised patients, as well as children with chronic diseases at greater risk of severe COVID-19 (neurological disorders and pulmonological, cardiovascular, genetic, and oncologic diseases), were more common in the oldest study group than in the toddler and infant groups. A lack of BCG vaccination was more frequent in infants than in toddlers and children.

The course of COVID-19 in all the study groups was analyzed in each of the first five pandemic waves caused by different SARS-CoV-2 variants. In Poland, the first wave of the COVID-19 pandemic occurred from March to June 2020, the second from October 2020 to January 2021, and then variants were not reported in Poland, and SARS-CoV-2 sequencing was performed only occasionally. In the third wave from February to May 2021, the alpha (B.1.1.7) variant dominated, in the fourth wave from 1 October 2021 to 15 January 2022, the delta (B.1.617.2) variant dominated, and in the fifth wave from 16 January to 30 April 2022, the omicron variant (B.1.1.529, BA.1, BA.1.1, BA.2, BA.3, BA.4, and BA.5 lineages) dominated.

Regarding the age groups affected during the particular COVID-19 pandemic waves, the greatest differences were found between the first and fifth waves (Figure 2). In the first wave, the majority of patients were older than five years (65/111 (58.5%) versus 22/111 (19.8%) in the infant group and 24/111 (21.6%) in the toddler group (p-value < 0.001)). In the fifth wave, the group of patients consisted of 192/411 (46.7%) infants, 152/411 (37%) toddlers, and 67/411 (16.3%) children older than five years. In the other waves, the differences between age groups were statistically insignificant, but it is noteworthy that, in the subsequent pandemic waves, the median age of the hospitalized patients decreased significantly.

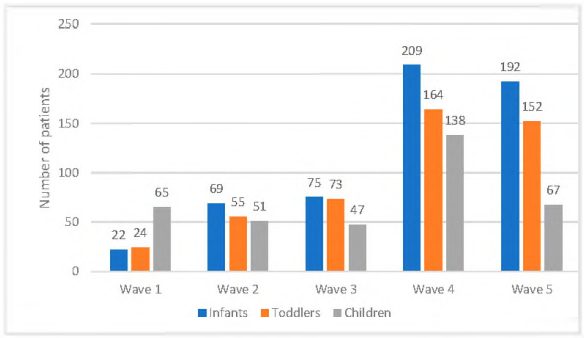


Figure 2. The number of patients in the groups of infants, toddlers, and children in the first five waves of the pandemic.

3.2. Clinical Presentation

The clinical presentation of COVID-19 in the study groups is presented in Table 2. In all age groups, fever was the most common sign of COVID-19, and it was most frequent in toddlers. As for respiratory symptoms, rhinitis was most common in infants and was rarely observed in children older than five years. Cough was less frequent in children than in the other two groups. Dyspnea was present in 11–15% of hospitalized children, with no significant differences between age groups. Anosmia and ageusia, the most typical symptoms of COVID-19, were rarely observed, and the differences between study groups were statistically insignificant. Neurologic symptoms (for example, seizures, paresis, vertigo) were most common in the children group.

Table 2. Clinical characteristics of COVID-19 in infants, toddlers, and children.

	Infants (n = 567)	Toddlers (n = 470)	Children (n = 368)	p-Value
Fever: n (%)	389 (69)	361 (77)	230 (63)	<0.001
Rhinitis: n (%)	295 (52)	201 (43)	112 (31)	<0.001
Cough: n (%)	317 (56)	273 (58)	178 (48)	0.014
Dyspnea: n (%)	61 (11)	50 (11)	56 (15)	0.080
Vomiting: n (%)	84 (15)	134 (29)	69 (19)	<0.001
Diarrhea: n (%)	126 (22)	129 (27)	56 (15)	<0.001
Anosmia n (%)	29 (5)	18 (4)	28 (8)	0.057
Ageusia: n (%)	30 (5)	18 (4)	26 (7)	0.12
Neurologic symptoms: n (%)	22 (4)	36 (8)	75 (21)	<0.001

3.3. Laboratory Findings

A comparison of laboratory findings in all the study groups is shown in Tables 3 and S1. C-Reactive Protein (CRP) was significantly higher in the group of toddlers. Leukopenia and thrombocytopenia were most frequently observed in older children. Significant differences between the groups were noted in the levels of parameters such as alanine transaminase, creatinine kinase, lactate dehydrogenase, and D-dimers. All of these parameters were highest in the infant group.

Table 3. Laboratory findings in hospitalized pediatric patients with COVID-19 according to age, based on the chi-square test.

	Infants (n = 567)	Toddlers (n = 470)	Children (n = 368)	p-Value
CRP > 5 mg/dL	129 (24)	224 (51)	154 (46)	<0.001
Leukocytes ($10^3/\mu L$)				
<4.5	29 (5)	32 (7)	88 (26)	
4.5–13.5	427	328	229	
>13.5	79 (15)	84 (19)	24 (7)	
Neutrophils ($10^3/\mu L$)				
<1.0	127 (25)	24 (6)	20 (6)	<0.001
1.0–6.5	359	308	259	
>6.5	30 (6)	99 (23)	50 (15)	
Lymphocytes ($10^3/\mu L$)				
<1.0	8 (2)	29 (7)	59 (18)	
1.0–7.0	373	371	266	
>7.0	136 (26)	32 (7)	1 (0.3)	
Blood platelets < 100,000/μL	4 (0.7)	9 (2)	10 (3)	0.050
Alanine transaminase > 54 U/L	48 (9)	13 (3)	13 (4)	<0.001
Creatinine kinase < 170 U/L	123 (28)	49 (13)	23 (8)	<0.001
Lactate dehydrogenase > 220 IU/L	454 (97)	335 (87)	105 (35)	<0.001
D-dimers > 500 ng/mL	305 (76)	161 (44)	106 (36)	<0.001

CRP. C-reactive protein.

3.4. COVID-19 Outcome

The COVID-19 outcome in the three study groups according to age was estimated based on four parameters: the necessity of oxygen therapy, intravenous rehydration treatment, general steroid therapy, and the length of hospitalization. The data are presented in Table 4.

Table 4. The disease outcome for 1405 hospitalized pediatric patients with COVID-19 according to age.

	Infants (n = 567)	Toddlers (n = 470)	Children (n = 368)	p-Value	Post-Hoc Analysis
Oxygen therapy: n (%)	11 (2)	10 (2)	17 (5)	0.043	
Intravenous fluids: n (%)	202 (36)	233 (50)	154 (42)	<0.001	
Steroid therapy: n (%)	28 (5)	49 (10)	27 (7)	0.004	
Length of stay (days) Median (25th–75th percentile)	4 (2–5)	3 (2–4)	3 (2–5)	0.021	1 vs. 2:0.006

Considering the fact that the study referred to hospitalized patients, the number of children requiring oxygen therapy was very low (2–5%) and was significantly the highest in the group of children older than five years. Intravenous rehydration was most frequently necessary in the group of toddlers, as was steroid therapy. The median length of hospitalization fluctuated between three and four days and was highest in infants.

A total of 14/1405 (1%) of our patients were treated with remdesivir based on Food and Drug Administration (FDA) and European Medicine Agency (EMA) recommendations [22,23]. Four of these patients were infants (1, 2, 8, and 11 months of age), and ten were children older than five years (9, 9, 12, 12, 15, 15, 15, 16, 16, and 18 years). A total of 3/1405 (0.2%) were treated with baricitinib according to FDA recommendations [24]. They were 7, 12, and 16 years of age.

3.5. Final Diagnoses

The most common diagnoses at the time of discharge from the hospital were upper and lower respiratory tract infections, gastroenterocolitis, and neurological syndromes. The differences between the age groups are presented in Table 5. The diagnosis of upper respiratory tract infection was most frequently made in the group of infants, and most patients suffered from laryngitis. We also observed otitis media in the course of COVID-19.

Table 5. Final diagnoses in hospitalized pediatric patients with COVID-19 according to age.

	Infants (n = 567)	Toddlers (n = 470)	Children (n = 368)	p-Value
Upper respiratory tract infection	355 (63)	280 (60)	188 (51)	0.002
Lower respiratory tract infection	137 (24)	140 (30)	124 (34)	0.005
Gastroenterocolitis	79 (14)	81 (17)	77 (21)	0.019
Neurological diagnoses	50 (9)	48 (10)	49 (13)	0.090
Other	101 (18)	82 (18)	69 (19)	0.881

Lower respiratory tract infection was rarer in the group of infants in comparison with the other groups. Pneumonia in teenagers resembled that in adults. The prevalence of gastroenterocolitis was highest in the group of children.

Neurological diagnoses were made in 9–13% of the pediatric patients, with no statistically significant differences between the study groups.

The most common other diagnoses were urinary tract infections, hepatitis, and skin lesions.

4. Discussion

From the beginning of the pandemic, age was reported as one of the most important risk factors for a severe course, hospitalization, and death due to COVID-19, which was confirmed in adults. However, regarding pediatric patients, some authors reported that the youngest children were most threatened by COVID-19 [15,16,25], and others reported that teenagers were more at risk [26–28].

4.1. Demographic Characteristics

Although children, if compared to adults, have a lower risk of a severe course of COVID-19, 1405 children were hospitalized and met the inclusion criteria for this analysis. It is noteworthy that the youngest children most commonly required hospitalization (Figure 1). In our study, patients in the first year of life constituted 40.35% of the sample, and children younger than five years accounted for 73.8% of the hospitalized patients with COVID-19 in this study. To the best of our knowledge, this is one of the first large single-center studies concerning only hospitalized pediatric patients with COVID-19 over two years of the pandemic. Other authors reported both hospitalized and ambulatory-treated children infected with SARS-CoV-2 and did not observe a predominance of the youngest children [15,17,29,30]. The results from the studies concerning inpatients and outpatients with COVID-19 were similar: 2.4–3.8% of children in the 0–1-year group and 39.1–35.9% in the 0–5-year group, according to the pandemic wave, were reported by Murugan et al. [29]. A total of 6.1% of patients in the 0–1 year group and 25.2% in the 0–5-year group were reported in Krajcar's study [17], and 35.1% of children aged 0–5 years were reported from Brazil [30]. A total of 45% of children in the 0–5-year group was reported in the SARSTer-PED study [15]. Among the hospitalized children, a huge prevalence of the youngest has been observed. Alteri reported from the period of the first four waves of the pandemic that, similar to our study results, 35.1% of hospitalized children with COVID-19 were 0–1 years old and 70.6% were 0–5 years old [16]. Swan reported from the United Kingdom (UK) that 52% of hospitalized children were 0–5 years old [31]. Recent CDC reports indicated that 22.5% of children hospitalized with COVID-19 were in the age range of 0–1 years, and 40.8% were aged 0–5 years [32]. There was also a significant increase in the percentage of pediatric patients younger than five years in hospital departments after the vaccination of children older than five years started [33]. Göktug observed in the Pediatric Emergency Department that 14.8% of patients were in the age range of 0–1 years compared to 32.4% in the 0–5-year range [27]. In our department, the predominance of the youngest children was much greater than that in the other reports, and we observed that, during the pandemic, the predominance of the youngest groups of children among hospitalized patients increased (Figure 2). Similar findings were reported by other authors [5,6,8]. Therefore, a difference between our study and those conducted previously was that this is the first study concerning a long period of time over the pandemic, from March 2020 to April 2022. This is also the reason for Alteri making this same observation. The increasing number of infants and toddlers among hospitalized patients with COVID-19 was probably due to the lifting of sanitary restrictions and the commencement of vaccination against COVID-19 for children older than five years, which caused a milder course and rarer need for hospitalization in older age groups. It is also noteworthy that patients with comorbidities and with immunodeficiency were the most numerous in the group of children older than five years, while the infants and toddlers often required hospitalization even though they had no chronic underlying conditions. This may be because the recommendations pointed to newborns and infants as being in the risk group for a severe course of COVID-19, causing more referrals of the youngest children to the hospital [21].

Comorbidities associated with the increased risk of severe disease mainly affected children older than five years (42.3%). Other researchers confirmed the same [34–36]. CDC reports also showed more underlying conditions among hospitalized pediatric patients aged 5–17 years (53.4%) and also, contrary to our findings, of 42.3% of patients in the youngest group (0–2 years of age) [37].

The differences between age groups in consecutive pandemic waves were of particular interest. The first wave was the only one in which the child group was the most numerous. In the next waves, the percentage of children decreased significantly. This was probably caused by the current Polish Health Ministry regulations. During the first wave and at the beginning of the second wave, hospitalization was obligatory for every patient who tested positive for SARS-CoV-2 by PCR. Only symptomatic patients were tested, and because of the strict lockdown, infants and toddlers were tested very rarely. At the beginning of the pandemic, the youngest children were infected the most often from a family member, while exposure other than household contacts was confirmed more frequently in teenagers [15]. Positive parents were isolated; they were not allowed to leave their houses, and there was no ability to have infants and toddlers tested up to the time hospitalization was necessary because of severe symptoms. In the fourth and fifth waves, vaccination against COVID-19 was possible for children older than five years, and it also had an influence on the age of hospitalized children [19–21].

The Bacillus Calmette-Guerin (BCG) vaccination parameter was also analyzed in this study (Table 1). This was due to the fact that, during the COVID-19 pandemic, it was hypothesized that countries without widespread tuberculosis prevention policies would have a higher percentage of severe disease course (Italy, France, Spain) than countries with long-term widespread prevention (Japan, Denmark, Korea) [38]. In Poland, according to The Obligatory Vaccination Schedule, the BCG vaccination is performed in the first days of life, which means that it was available to all children included in the study. The highest number of unvaccinated BCG patients was the group of infants whose disease severity required admission to the hospital, although they had the fewest underlying medical conditions. Nevertheless, fewer infants may be vaccinated against BCG in the general population. This needs further investigation.

4.2. Clinical Presentation and Final Diagnoses

The clinical presentation of COVID-19 in hospitalized children was multisymptomatic in all age groups. The most frequent symptoms were fever, cough, and rhinitis, especially in infants and toddlers. These symptoms were also described by other authors [25,32,39–43]. In infants, cough and dyspnea were more common symptoms of upper respiratory tract infection, and the most common symptom was laryngitis (Table 5). We also observed otitis media in the course of COVID-19. Similar observations were reported by other researchers [25]. High fever, vomiting, and diarrhea were observed much more frequently in patients aged 0–5 years. These symptoms influenced the need for hospitalization and intravenous rehydration but did not cause a severe and life-threatening course of the disease. In many previous publications, the authors reported gastrointestinal symptoms (vomiting, diarrhea, and abdominal pain) as typical for pediatric patients and more often in younger children [15,25,28,31,39,40,42,44]. Nevertheless, there are some publications reporting a low percentage of gastrointestinal symptoms in hospitalized children [41,45]. Because these same signs and symptoms can appear in different diseases, we also analyzed the diagnoses at discharge from the hospital. This seems to be important because, e.g., vomiting can appear in the course of gastroenterocolitis but also in neurological diseases and even during pneumonia and upper respiratory tract infections. It is interesting that gastroenterocolitis in our cohort was diagnosed as most common in children older than five years. Previous research usually did not consider final diagnoses, focusing on signs and symptoms; thus, it is not possible to compare our observations to those in other studies.

Neurologic symptoms were significantly more common in the group of children older than five years, similar to other authors' reports [46,47].

Based on statistical data, it seems that anosmia and ageusia are more common in children older than five years, but this is difficult to analyze because toddlers and infants cannot verbalize such symptoms. It is noteworthy that, in our study, infants and toddlers most often required intravenous rehydration, although we did not observe relevant ongoing fluid losses. This might have been because of anosmia and ageusia. Many authors

confirmed that the main problem is that symptoms related to taste and smell are so subjective that it is difficult to assess them in pediatric age groups [48]. Nevertheless, Yan et al., in an analysis of 18 eligible studies, also concluded that higher smell or taste dysfunction rates were associated with a younger age [49].

4.3. Laboratory Findings

Differences between the three studied groups were found in the laboratory test results (Tables S1 and 3). Most abnormalities appeared in the infant group; they were temporary and did not differ significantly from those of other viral diseases. Although changes in laboratory results have been widely described in adults and in children with COVID-19, there are only a few studies concerning laboratory findings in hospitalized pediatric patients according to age. Similar to our observations, they have all reported leucopenia, neutropenia, lymphocytosis, thrombocytopenia, and elevated CRP, CK, LDH, ALT, and D-dimers as typical in most pediatric patients with COVID-19, especially in patients 0–5 years old [29,40,41,50,51]. Nevertheless, some publications show a relationship between the laboratory parameters at admission and hospitalization and the patient's prognosis at every age. They showed that severe cases had significantly higher levels of mean serum lactate, CRP, ALT, and D-dimers, and an increase in LDH was observed even in asymptomatic patients [40,45,51].

4.4. Disease Outcome

According to other reports, 9–54% of hospitalized pediatric patients with COVID-19 required oxygen support [29,32,44,52], while, in our department, only 2% of infants and toddlers and 5% of children older than five years required this intervention. This difference could have been because infants were hospitalized with a much milder course of COVID-19 than older children because of the recommendations that infants be considered at a high risk of a severe course of the disease [21]. One patient in our department required high-flow nasal oxygen therapy (HFNOT), only three (0.2% of our cohort, 0.8% of the children group) had to be referred to the Pediatric Intensive Care Unit (PICU), and no patients died. All four patients with the most severe course of COVID-19 were older than 10 years, and all had chronic diseases (cerebral palsy, genetic disorders, and critical obesity). These data significantly departed from those of other authors, who reported that up to 21% of patients required PICU admission [28,31,45]. This can be explained by the higher percentage of infants and toddlers in our cohort and by the fact that almost all of our patients were of white Caucasian ethnicity, while in numerous reports, it was revealed that greater disease severity was associated with Black or other non-White races and ages older than four years [31,53,54].

The median length of hospitalization in our cohort was 3–4 days and was significantly longer in the group of infants. In other publications, the authors reported shorter hospitalization. Swann from U.K. and Cloete from South Africa reported an average two-day stay [31,44]. Other authors reported much longer stays exceeding 10 days [11,40]. Hospitalization was significantly longer in the group of infants, similar to other authors' reports [11,15,25,40].

Our study had several limitations. At the beginning of the pandemic, primary care for COVID-19 patients was limited; thus, they were often referred to the hospital. The recommendations regarding the rules for COVID-19 testing, isolation, and hospitalization changed, and this could have influenced the admission criteria and the length of hospitalization. Our experience with pediatric COVID-19 also increased during the pandemic, which could have influenced hospital admissions and the length of stay.

To the best of our knowledge, this is the first large single-center study comparing the differences between the clinical course of pediatric hospitalized COVID-19 patients in different age groups for more than two years of the pandemic.

5. Conclusions

Many statistically significant differences in disease signs and symptoms were observed between study groups. Infants were the most often hospitalized patients in the first two years of the pandemic. The reasons for infant hospitalization were the necessity of intravenous rehydration because of dehydration in the course of high fever, vomiting and diarrhea, and appetite disorders.

Severe courses requiring oxygen supplementation and antiviral therapy were more common in adolescents.

A total of 74% of the hospitalized patients with COVID-19 were younger than five years, with a growing trend in the subsequent waves, most likely due to vaccination rolling out to the older age groups.

Supplementary Materials: The following supporting information can be downloaded at: https://www.mdpi.com/article/10.3390/jcm11247347/s1, Table S1: Laboratory findings in hospitalized pediatric patients with COVID-19 according to age, based on the Kruskal–Wallis test.

Author Contributions: Conceptualization, L.S. and P.K.; methodology, L.S. and P.K.; investigation, L.S., P.K., A.K., I.M., J.S. (Justyna Stala), J.S. (Justyna Szebla) and M.J.; data interpretation, L.S. and P.K.; writing—original draft preparation, L.S., P.K. and A.K.; supervision: L.S. and P.K. All authors have read and agreed to the published version of the manuscript.

Funding: This research received no external funding.

Institutional Review Board Statement: This study was conducted in accordance with the Declaration of Helsinki and was approved by the Institutional Ethics Committees. Name of the Ethics Committee: Regional Medical Chamber in Krakow, No. OIL/KBL/18/2020.

Informed Consent Statement: Not applicable.

Data Availability Statement: The datasets used and analyzed during the current study are available from the corresponding author upon reasonable request.

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

References

1. Lu, R.; Zhao, X.; Li, J.; Niu, P.; Yang, B.; Wu, H.; Wang, W.; Song, H.; Huang, B.; Zhu, N.; et al. Genomic characterisation and epidemiology of 2019 novel coronavirus: Implications for virus origins and receptor binding. *Lancet* **2020**, *395*, 565–574. [CrossRef] [PubMed]
2. Zimmermann, P.; Curtis, N. Why is COVID-19 less severe in children? A review of the proposed mechanisms underlying the age-related difference in severity of SARS-CoV-2 infections. *Arch. Dis. Child.* **2021**, *106*, 429–439. [CrossRef] [PubMed]
3. Flisiak, R.; Rzymski, P.; Zarębska-Michaluk, D.; Rogalska, M.; Rorat, M.; Czupryna, P.; Lorenc, B.; Ciechanowski, P.; Kozielewicz, D.; Piekarska, A.; et al. Demographic and Clinical Overview of Hospitalized COVID-19 Patients during the First 17 Months of the Pandemic in Poland. *J. Clin. Med.* **2021**, *11*, 117. [CrossRef] [PubMed]
4. O'Driscoll, M.; Ribeiro Dos Santos, G.; Wang, L.; Cummings, D.A.T.; Azman, A.S.; Paireau, J.; Fontanet, A.; Cauchemez, S.; Salje, H. Age-specific mortality and immunity patterns of SARS-CoV-2. *Nature* **2021**, *590*, 140–145. [CrossRef]
5. Coronavirus (COVID-19) Latest Insights: Deaths. Available online: https://www.ons.gov.uk/peoplepopulationandcommunity/healthandsocialcare/conditionsanddiseases/articles/coronaviruscovid19latestinsights/deaths#deaths-by-age (accessed on 24 September 2022).
6. CDC Data. Available online: https://data.cdc.gov/d/9bhg-hcku/visualization (accessed on 24 September 2022).
7. Global Excess Deaths Associated with COVID-19 (Modelled Estimates). Available online: https://www.who.int/data/sets/global-excess-deaths-associated-with-COVID-19-modelled-estimates (accessed on 24 September 2022).
8. Demographic Trends of COVID-19 Cases and Deaths in the US Reported to CDC. Available online: www.cdc.gov/covid-data-tracker/index.html#demographics (accessed on 14 September 2022).
9. Lu, X.; Zhang, L.; Du, H.; Zhang, J.; Li, Y.; Qu, J.; Zhang, W.; Wang, Y.; Bao, S.; Li, Y.; et al. SARS-CoV-2 Infection in Children. *N. Engl. J. Med.* **2020**, *382*, 1663–1665. [CrossRef] [PubMed]
10. Castagnoli, R.; Votto, M.; Licari, A.; Brambilla, I.; Bruno, R.; Perlini, S.; Rovida, F.; Baldanti, F.; Marseglia, G.L. Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) Infection in Children and Adolescents: A Systematic Review. *JAMA Pediatr.* **2020**, *174*, 882–889. [CrossRef]

11. Badal, S.; Thapa Bajgain, K.; Badal, S.; Thapa, R.; Bajgain, B.B.; Santana, M.J. Prevalence, clinical characteristics, and outcomes of pediatric COVID-19: A systematic review and meta-analysis. *J. Clin. Virol. Off. Publ. Pan. Am. Soc. Clin. Virol.* **2021**, *135*, 104715. [CrossRef]
12. Turan, C.; Basa, E.G.; Elitez, D.; Yılmaz, Ö.; Gümüş, E.; Anıl, M. The Comparison of Children Who Were Diagnosed with COVID-19 in the First and the Second Waves of the SARS-CoV-2 Pandemic. *Turk. Arch. Pediatr.* **2021**, *56*, 596–601. [CrossRef]
13. Chua, G.T.; Wong, J.S.C.; Lam, I.; Ho, P.P.K.; Chan, W.H.; Yau, F.Y.S.; Duque, J.S.R.; Ho, A.C.C.; Siu, K.K.; Cheung, T.W.Y.; et al. Clinical Characteristics and Transmission of COVID-19 in Children and Youths During 3 Waves of Outbreaks in Hong Kong. *JAMA Netw. Open* **2021**, *4*, e218824. [CrossRef]
14. Butt, A.A.; Dargham, S.R.; Loka, S.; Shaik, R.M.; Chemaitelly, H.; Tang, P.; Hasan, M.R.; Coyle, P.V.; Yassine, H.M.; Al-Khatib, H.A.; et al. COVID-19 Disease Severity in Children Infected with the Omicron Variant. *Clin. Infect. Dis.* **2022**, *75*, e361–e367. [CrossRef]
15. Pokorska-Śpiewak, M.; Talarek, E.; Mania, A.; Pawłowska, M.; Popielska, J.; Zawadka, K.; Figlerowicz, M.; Mazur-Melewska, K.; Faltin, K.; Ciechanowski, P.; et al. Clinical and Epidemiological Characteristics of 1283 Pediatric Patients with Coronavirus Disease 2019 during the First and Second Waves of the Pandemic—Results of the Pediatric Part of a Multicenter Polish Register SARSTer. *J. Clin. Med.* **2021**, *10*, 5098. [CrossRef] [PubMed]
16. Alteri, C.; Scutari, R.; Costabile, V.; Colagrossi, L.; Yu La Rosa, K.; Agolini, E.; Lanari, V.; Chiurciu, S.; Romani, L.; Markowich, A.H.; et al. Epidemiological characterization of SARS-CoV-2 variants in children over the four COVID-19 waves and correlation with clinical presentation. *Sci. Rep.* **2022**, *12*, 10194. [CrossRef]
17. Krajcar, N.; Stemberger Marić, L.; Šurina, A.; Kurečić Filipović, S.; Trkulja, V.; Roglić, S.; Tesović, G. Epidemiological and clinical features of Croatian children and adolescents with a PCR-confirmed coronavirus disease 2019: Differences between the first and second epidemic wave. *Croat. Med. J.* **2020**, *61*, 491–500. [CrossRef] [PubMed]
18. WHO. Recommendations for National SARS-CoV-2 Testing Strategies and Diagnostic Capacities. Available online: https://www.who.int/publications/i/item/WHO-2019-nCoV-lab-testing-2021.1-eng (accessed on 24 August 2022).
19. Polish National Institute of Public Health. Recommendations on SARS-CoV2 Laboratory Diagnostics. Available online: https://www.pzh.gov.pl/koronawirus-sars-cov-2/wytyczne-i-rekomendacje/ (accessed on 24 August 2022).
20. Regulation of the Polish Minister of Health from 16 March 2020. Available online: https://legislacja.rcl.gov.pl/projekt/12331301/katalog/12669385#12669385 (accessed on 24 August 2022).
21. Marczyńska, M.; Figlerowicz, M.; Kalicki, B.; Kuchar, E.; Majda-Stanisławska, E.; Pawłowska, M.; Sulik, A.; Sybilski, A.; Szenborn, L.; Wysocki, J.; et al. Management of a Child with COVID-19 Recommendations for Pediatricians and Family Medicine Physicians in Primary Healthcare and Hospital Settings. Available online: https://ptp.edu.pl/dokumenty/covid/post_z_dzieckiem_covid-19.pdf (accessed on 21 July 2022).
22. EMA Summary of Product Characteristics Veklury 100 mg. Available online: https://www.ema.europa.eu/en/documents/other/veklury-product-information-approved-chmp-25-june-2020-pending-endorsement-european-commission_en.pdf (accessed on 24 August 2022).
23. Fact Sheet for Healthcare Providers Emergency Use Authorization (EUA) of Veklury® (Remdesivir) for the Treatment of Coronavirus Disease 2019 (COVID-19) in Pediatric Patients Weighing 3.5 kg to Less than 40 kg or Pediatric Patients Less than 12 Years of Age Weighing at Least 3.5 kg, with Positive Results of Direct SARS-CoV-2 Viral Testing Who Are: Hospitalized, or Not Hospitalized and Have Mild-to-Moderate COVID-19, and Are at High Risk for Progression to Severe COVID-19, Including Hospitalization or Death. Available online: https://www.fda.gov/media/137566/download (accessed on 24 August 2022).
24. CHKD Treatment Guideline for COVID-19 in Children. Available online: https://www.chkd.org/uploadedFiles/Documents/COVID-19/CHKD%20COVID%2019%20treatment%20guideline.pdf (accessed on 24 August 2022).
25. Sobolewska-Pilarczyk, M.; Pokorska-Śpiewak, M.; Stachowiak, A.; Marczyńska, M.; Talarek, E.; Oldakowska, A.; Kucharek, I.; Sybilski, A.; Mania, A.; Figlerowicz, M.; et al. COVID-19 infections in infants. *Sci. Rep.* **2022**, *12*, 7765. [CrossRef] [PubMed]
26. Preston, L.E.; Chevinsky, J.R.; Kompaniyets, L.; Lavery, A.M.; Kimball, A.; Boehmer, T.K.; Goodman, A.B. Characteristics and Disease Severity of US Children and Adolescents Diagnosed With COVID-19. *JAMA Netw. Open* **2021**, *4*, e215298. [CrossRef] [PubMed]
27. Göktug, A.; Güngör, A.; Öz, F.N.; Akelma, Z.; Güneylioglu, M.M.; Yaradılmıs, R.M.; Bodur, I.; Öztürk, B.; Tekeli, A.; Karacan, C.D.; et al. Evaluation of Epidemiological, Demographic, Clinical Characteristics and Laboratory Findings of COVID-19 in the Pediatric Emergency Department. *J. Trop. Pediatr.* **2021**, *67*, fmab066. [CrossRef] [PubMed]
28. Webb, N.E.; Osburn, T.S. Characteristics of Hospitalized Children Positive for SARS-CoV-2: Experience of a Large Center. *Hosp. Pediatr.* **2021**, *11*, e133–e141. [CrossRef]
29. Murugan, P.T.; Ghosh, U.; Rajan, R.J.; Punnen, A.; Chandran, J.; Das Adhikari, D.; Mathew, L.G.; Rose, W. Spectrum of COVID-19 Disease in Children: A Retrospective Analysis Comparing Wave 1 and Wave 2 from a Tertiary Hospital in South India. *Indian J. Pediatr.* **2022**, *89*, 1222–1228. [CrossRef]
30. Carvalho, M.S.; Bastos, L.S.; Fuller, T.; Cruz, O.G.; Damasceno, L.; Calvet, G.; Resende, P.C.; Smith, C.; Whitworth, J.; Siqueira, M.; et al. Incidence of SARS-CoV-2 over four epidemic waves in a low-resource community in Rio de Janeiro, Brazil: A prospective cohort study. *Lancet Reg. Health Am.* **2022**, *12*, 100283. [CrossRef]

31. Swann, O.V.; Pollock, L.; Holden, K.A.; Munro, A.P.S.; Bennett, A.; Williams, T.C.; Turtle, L.; Fairfield, C.J.; Drake, T.M.; Faust, S.N.; et al. Comparison of UK paediatric SARS-CoV-2 admissions across the first and second pandemic waves. *Pediatr. Res.* **2022**, 1–10. [CrossRef]
32. Wanga, V.; Gerdes, M.E.; Shi, D.S.; Choudhary, R.; Dulski, T.M.; Hsu, S.; Idubor, O.I.; Webber, B.J.; Wendel, A.M.; Agathis, N.T.; et al. Characteristics and Clinical Outcomes of Children and Adolescents Aged <18 Years Hospitalized with COVID-19—Six Hospitals, United States, July–August 2021. *MMWR Morb. Mortal. Wkly. Rep.* **2021**, *70*, 1766–1772. [CrossRef]
33. Laboratory Confirmed COVID-19-Associated Hospitalizations. Available online: https://gis.cdc.gov/grasp/COVIDNet/COVID19_5.html#virusTypeDiv (accessed on 14 September 2022).
34. Ward, J.L.; Harwood, R.; Smith, C.; Kenny, S.; Clark, M.; Davis, P.J.; Draper, E.S.; Hargreaves, D.; Ladhani, S.; Linney, M.; et al. Risk factors for PICU admission and death among children and young people hospitalized with COVID-19 and PIMS-TS in England during the first pandemic year. *Nat. Med.* **2022**, *28*, 193–200. [CrossRef] [PubMed]
35. Harwood, R.; Yan, H.; Talawila Da Camara, N.; Smith, C.; Ward, J.; Tudur-Smith, C.; Linney, M.; Clark, M.; Whittaker, E.; Saatci, D.; et al. Which children and young people are at higher risk of severe disease and death after hospitalisation with SARS-CoV-2 infection in children and young people: A systematic review and individual patient meta-analysis. *eClinicalMedicine* **2022**, *44*, 101287. [CrossRef]
36. Widjanarko, M.; Nindya, M.; Fernandez, G.; Jovito, A. Comorbidities and COVID-19 severity in pediatric patients: Systematic review and meta-analysis. *PI* **2022**, *62*, 51–60. [CrossRef]
37. Kim, L.; Whitaker, M.; O'Halloran, A.; Kambhampati, A.; Chai, S.J.; Reingold, A.; Armistead, I.; Kawasaki, B.; Meek, J.; Yousey-Hindes, K.; et al. Hospitalization Rates and Characteristics of Children Aged <18 Years Hospitalized with Laboratory-Confirmed COVID-19—COVID-NET, 14 States, March 1–July 25, 2020. *MMWR Morb. Mortal. Wkly. Rep.* **2020**, *69*, 1081–1088. [CrossRef]
38. Czajka, H.; Zapolnik, P.; Krzych, Ł.; Kmiecik, W.; Stopyra, L.; Nowakowska, A.; Jackowska, T.; Darmochwał-Kolarz, D.; Szymański, H.; Radziewicz-Winnicki, I.; et al. A Multi-Center, Randomised, Double-Blind, Placebo-Controlled Phase III Clinical Trial Evaluating the Impact of BCG Re-Vaccination on the Incidence and Severity of SARS-CoV-2 Infections among Symptomatic Healthcare Professionals during the COVID-19 Pandemic in Poland-First Results. *Vaccines* **2022**, *10*, 314. [CrossRef]
39. García-Vera, C.; Castejón-Ramírez, S.; Laín Miranda, E.; Hernández Abadía, R.; García Ventura, M.; Borque Navarro, E.; Rubio Sánchez, P.; Baeta Ruiz, A.; Mengual Gil, J.M. COVID-19 in children: Clinical and epidemiological spectrum in the community. *Eur. J. Pediatr.* **2022**, *181*, 1235–1242. [CrossRef] [PubMed]
40. Guler, M.A.; Laloglu, F.; Orbak, Z.; Ceviz, N.; Islek, A. Clinical Features of Children with COVID-19 Infection: Single-Center Experience. *Eurasian J. Med.* **2022**, *54*, 173–180. [CrossRef] [PubMed]
41. Kepenekli, E.; Yakut, N.; Ergenc, Z.; Aydıner, Ö.; Sarınoglu, R.C.; Karahasan, A.; Karakoc-Aydıner, E.; Memişoglu, A.; Gökdemir, Y.; Eralp, E.E.; et al. COVID-19 disease characteristics in different pediatric age groups. *J. Infect. Dev. Ctries.* **2022**, *16*, 16–24. [CrossRef] [PubMed]
42. Najafinejad, M.; Cheraghali, F.; Aghcheli, B.; Rajabi, A.; Barati, L.; Naziri, H.; Gharib, M.H.; Tabarraei, A.; Nakstad, B.; Tahamtan, A. COVID-19 in Pediatrics: Demographic, Clinical, Laboratory, and Radiological Characteristics of Infected Patients with SARS-CoV-2. *Front. Pediatr.* **2022**, *9*, 808187. [CrossRef]
43. De Filippo, M.; Magri, P.; Bossi, G.; Brambilla, I.; Castagnoli, R.; Mascolo, A.; Votto, M.; Licari, A.; Marseglia, G.L. Clinical and Epidemiological Features of Pediatric Patients with COVID-19 in a Tertiary Pediatric Hospital. *Acta Biomed.* **2022**, *93*, e2022039. [CrossRef] [PubMed]
44. Cloete, J.; Kruger, A.; Masha, M.; du Plessis, N.M.; Mawela, D.; Tshukudu, M.; Manyane, T.; Komane, L.; Venter, M.; Jassat, W.; et al. Paediatric hospitalisations due to COVID-19 during the first SARS-CoV-2 omicron (B.1.1.529) variant wave in South Africa: A multicentre observational study. *Lancet Child Adolesc. Health* **2022**, *6*, 294–302. [CrossRef] [PubMed]
45. Zachariah, P.; Johnson, C.L.; Halabi, K.C.; Ahn, D.; Sen, A.I.; Fischer, A.; Banker, S.L.; Giordano, M.; Manice, C.S.; Diamond, R.; et al. Columbia Pediatric COVID-19 Management Group. Epidemiology, Clinical Features, and Disease Severity in Patients With Coronavirus Disease 2019 (COVID-19) in a Children's Hospital in New York City, New York. *JAMA Pediatr.* **2020**, *174*, e202430. [CrossRef] [PubMed]
46. Ray, S.T.J.; Abdel-Mannan, O.; Sa, M.; Fuller, C.; Wood, G.K.; Pysden, K.; Yoong, M.; McCullagh, H.; Scott, D.; McMahon, M.; et al. Neurological manifestations of SARS-CoV-2 infection in hospitalised children and adolescents in the UK: A prospective national cohort study. *Lancet Child Adolesc. Health* **2021**, *5*, 631–641. [CrossRef] [PubMed]
47. Dilber, B.; Aydın, Z.G.G.; Yesilbas, O.; Sag, E.; Aksoy, N.K.; Gündogmus, F.; Küçükalioglu, B.P.; Yılmaz, S.A.; Demirhan, Y.N.; Çelik, N.; et al. Neurological Manifestations of Pediatric Acute COVID Infections: A Single Center Experience. *J. Trop. Pediatr.* **2021**, *67*, fmab062. [CrossRef] [PubMed]
48. Erdede, O.; Sarı, E.; Uygur Külcü, N.; Uyur Yalçın, E.; Sezer Yamanel, R.G. An overview of smell and taste problems in paediatric COVID-19 patients. *Acta Paediatr.* **2020**, *109*, 2184–2186. [CrossRef]
49. Yan, Q.; Qiu, D.; Liu, X.; Guo, X.; Hu, Y. Prevalence of Smell or Taste Dysfunction Among Children With COVID-19 Infection: A Systematic Review and Meta-Analysis. *Front. Pediatr.* **2021**, *9*, 686600. [CrossRef]
50. Zimmermann, P.; Curtis, N. Coronavirus Infections in Children Including COVID-19: An Overview of the Epidemiology, Clinical Features, Diagnosis, Treatment and Prevention Options in Children. *Pediatr. Infect. Dis. J.* **2020**, *39*, 355–368. [CrossRef]

51. Yasuhara, J.; Kuno, T.; Takagi, H.; Sumitomo, N. Clinical characteristics of COVID-19 in children: A systematic review. *Pediatr. Pulmonol.* **2020**, *55*, 2565–2575. [CrossRef]
52. Mania, A.; Faltin, K.; Mazur-Melewska, K.; Małecki, P.; Jończyk-Potoczna, K.; Lubarski, K.; Lewandowska, Z.; Cwalińska, A.; Rosada-Kurasińska, J.; Bartkowska-Śniatkowska, A.; et al. Clinical Picture and Risk Factors of Severe Respiratory Symptoms in COVID-19 in Children. *Viruses* **2021**, *13*, 2366. [CrossRef]
53. Woodruff, R.C.; Campbell, A.P.; Taylor, C.A.; Chai, S.J.; Kawasaki, B.; Meek, J.; Anderson, E.J.; Weigel, A.; Monroe, M.L.; Reeg, L. Risk Factors for Severe COVID-19 in Children. *Pediatrics* **2022**, *149*, e2021053418. [CrossRef] [PubMed]
54. Antoon, J.W.; Grijalva, C.G.; Thurm, C.; Richardson, T.; Spaulding, A.B.; Teufel, R.J., 2nd; Reyes, M.A.; Shah, S.S.; Burns, J.E.; Kenyon, C.C. Factors Associated With COVID-19 Disease Severity in US Children and Adolescents. *J. Hosp. Med.* **2021**, *16*, 603–610. [CrossRef] [PubMed]

6.3. Publikacja trzecia

Risk factors of severe course and fatality in children hospitalized for COVID-19 – two centers cohort study

Lidia Stopyra[1,2], Aleksandra Kowalik[3], Łukasz Wentrys[3], Przemko Kwinta[3].

1. Department of Infectious Diseases and Pediatrics, S. Żeromski Specialist Hospital in Krakow, Poland
2. Andrzej Frycz Modrzewski Krakow Academy, Poland
3. Department of Pediatrics, Jagiellonian University Medical College, Poland

Abstract

Introduction

After three years of the pandemic, predictors of COVID-19 severity in children are still not completely known. This study was designed to define the high-risk group in hospitalized children.

Material and methods

The analysis covered 2338 children in two centers. Among patients with severe course three groups were identified – requiring and not requiring mechanical ventilation and those who died.

Results

The median age of seventy children (54% female) with severe COVID-19 was 32 months. In 43 (61%) children comorbidities were present. No one was vaccinated against COVID-19. On admission, medium SpO2 was 89%. 65 (93%) patients presented with dyspnoea, and 49 (70%) with cough. 53 (76%) children required noninvasive oxygen support and 17 (24%) mechanical ventilation. 8(11%) children died. The most significant difference between mechanically ventilated children who recovered and those who died was age – 124 vs 12.8 months ($p<0.001$). Children requiring mechanical ventilation presented higher CRP (median 33.4 vs 6.7 mg/dl), LDH, and ferritin. In children who died even higher CRP (55.9 vs 7.9 mg/dl), deep lymphopenia (0.65 vs 1.85 x 103/ul), and thrombocytopenia (7 vs 237 x 103/ul) were observed.

Conclusions

Risk factors for a severe course of COVID-19 were – young age, lack of COVID-19 vaccination, auscultation changes and dyspnea at admission. The presence of comorbidities, high CRP, LDH, and ferritin levels were the predictors of mechanical ventilation necessity and death. Among children mechanically ventilated teenagers had a prognosis of recovery but, infants with comorbidities were at the highest risk of death.

Introduction

In December 2019, a cluster of severe, life-threatening cases of pneumonia was detected in China, caused by severe acute respiratory syndrome coronavirus (SARS-CoV-2). On 11 March 2020, the World Health Organization (WHO) announced the Coronavirus Disease 2019 (COVID-19) pandemic.

Since the beginning of the pandemic, children have been reported all over the world to present with an asymptomatic or mild course of the disease [1-3].

However, it has been shown that chronic background illnesses including heart disease, chronic lung disease, and/or asthma, developmental delay, diabetes, immune compromise, malignancy, and obesity, can trigger severe COVID-19 also in children [4]. SARS-CoV-2-related death in children is rare. In the United States, as of February 2023, there were >16 million cases of COVID-19 and 2098 COVID-19-associated deaths in children <18 years of age (<0.01%) reported to the Center for Disease Control and Prevention (CDC) [5].

This work aimed to analyze the COVID-19 course in pediatric severely ill patients, hospitalized from March 2020 to September 2022. The analysis was conducted especially in terms of clinical presentation, laboratory findings, and outcomes. The study was designed to find the possibilities for the prediction of the severity of COVID-19 in hospitalized children.

Materials and Methods

„Because of the COVID-19 pandemic announced by the WHO and the increasing incidence in Poland, the Department of Infectious Diseases and Paediatrics was ordered to treat children with COVID-19. The University Children's Hospital was selected to provide highly specialised diagnosis and treatment, if necessary. These organizational solutions centralized the care for children with COVID-19 in the southern region of Poland".

On 23 March 2020, the first children with COVID-19 were admitted to the hospital, and the prospective study was started. Up to 30 September 2022, 2338 children were hospitalized.

Data were collected in all successively admitted patients, based on a standard protocol. On admission, after taking the medical history and performing a physical examination, a planned set of laboratory tests was taken in all patients, including complete blood count (CBC) parameters, C-reactive protein (CRP), alanine transaminase (ALT), lactate dehydrogenase (LDH), creatine kinase (CK), ferritin, procalcitonin (PCT). All children with severe course of COVID-19 had imaging tests taken (i.e., lung ultrasound (LU), chest X-ray, and high-resolution computed tomography (HRCT)). All children were subject to careful medical observation and treatment in accordance with current guidelines. Data on the course of hospitalization was also recorded in a planned and strictly structured manner in a specially designed database (the length of hospitalization, the length of oxygen treatment, antiviral treatment, systemic steroid therapy, pediatric intensive care unit (PICU) admission, respiratory therapy, and deaths).

Definitions

Owing to the absence of a consensus definition of the disease's severity in children, different definitions have been used in studies categorizing its level [6]. In this study, we used severity classification for acute SARS-CoV-2 infection provided in the multicenter interim guidance on the use of antivirals for children with COVID-19 [4], [7].

The severe case was diagnosed in a patient with pneumonia, age 0–18 years, laboratory-confirmed COVID-19, and a new requirement for supplemental oxygen or increased requirement from baseline without new or increased need for ventilatory support (noninvasive or invasive). Patients diagnosed with Multisystem Inflammatory Syndrome in Children (MIS-C) were excluded.

According to the WHO and the National Institute of Public Health recommendations [8], [9] COVID-19 was diagnosed using a positive reverse transcription and real-time polymerase chain

reaction (RT-PCR) and, since 30 October 2020, using the second-generation antigen tests based on a nasopharyngeal swab performed in certified laboratories.

Radiographic and ultrasonographic (USG) pneumonia diagnoses were based on the interpretation by the treating physician. Lower respiratory infections were diagnosed based on clinical presentation, LU, chest X-rays, and HRCT.

Remdesivir was used in our departments according to the Food and Drug Administration's (FDA) and European Medicines Agency's (EMA's) recommendations [10], [11].

Statistical analysis plan

In the first stage of the analysis, the population of children with severe COVID-19 was described in detail. Next, among children diagnosed with severe COVID-19, the following subgroups of patients were identified for further analysis: 1) children with severe COVID-19, who did not require mechanical ventilation and 2) children requiring mechanical ventilation. In addition, while evaluating the collected data, it was decided to select a third subgroup of patients for analysis - children who died due to severe COVID-19. In the final stage of the analysis, the data of children with severe COVID-19 was also compared with the data of children hospitalized due to COVID-19, but who did not meet the criteria for severe COVID-19. To reduce the risk of error associated with the lack of complete data, data from only one center were included in the analysis in this part of the study. The data for comparison came from the register of COVID-19 patients previously published by the authors of the study and included 1407 patients hospitalized between March 2020 and April 2022.

The statistical analysis was performed using SPSS ver. 27 software (Armonk, NY, USA). Results were presented based on the parameters of descriptive statistics, including the mean values and standard deviations (SD) for the quantitative variables with a normal distribution or median values with the interquartile range for non-normally distributed data. Categorical variables were presented as numbers with percentages. Qualitative values were compared by the chi-square test. The Kruskal–Wallis test was used for the analysis of the continuous variables investigated in the study. In all cases

of statistical significance, a pairwise comparison between the groups was performed using a post-hoc test. In all analyses, a p-value < 0.05 was considered statistically significant.

The study was performed in accordance with the ethical standards of the Declaration of Helsinki and its later amendments. It was approved by the Ethics Committee of the Regional Medical Chamber in Krakow No OIL/KBL/18/2020 on 10 March 2020.

Results

Characteristics of children with severe COVID-19

70 among 2338 children hospitalized in two centers (3%) met the criteria of COVID-19 severe course. The median age was 32.65 with a slight female prevalence (54%). In 43 (61%) comorbidities were present. The most often neurological (26%), cardiological (14%), genetic diseases (11%), and obesity appeared. 9 (13%) of patients had multiple underlying conditions. On admission medium SpO2 was 89%; 65 patients (93%) presented with dyspnoea, 49 (70%) with cough, 31 (44%) with neurological symptoms, and 34 (49%) with dehydration. The medium length of stay was 13.9 days. 27 patients (37%) required admission to the PICU and 8 (11%) died. Although the vaccination against COVID-19 was available in Poland from 7 June 2021 for 12-15 year-olds and from 4 December 2021 for 5-11 year-olds, nobody in our cohort was vaccinated.

Risk factors for the need for mechanical ventilation in children with severe COVID-19

Among 70 children with severe COVID-19, 53 (76%) required passive oxygen therapy and 17(24%) mechanical ventilation. A comparison of selected demographic and clinical data in the groups of children not requiring and requiring ventilator therapy is presented in Table I.

Table I. Characteristics of children not requiring and requiring mechanical ventilation.

	Children not requiring mechanical ventilation (n=53) (76%)	Children requiring mechanical ventilation (n=17) (24%)	p-value
Demographic data			
Age (months) - Me; (IQR)	34.2 (9.3-168)	27.6 (8.9-124)	0.52*
Sex (male/female)	24/28	7/10	0.784**
Chronic illness (n/%)	28 (53)	15 (94)	0.003**
Clinical data at admission			
Day from the onset of symptoms (days)	4 (2-6)	3 (1-3)	0.12*
Cough (n/%)	43 (81)	6 (35)	<0.001**
Dyspnea (n/%)	50 (94)	15 (88)	0.59**
Dehydration (n/%)	31 (59)	3 (19)	0.01**
Neurologic symptoms (n/%)	24 (45)	7 (41)	1.0**
SpO2 at admission (%)	88 (84-90)	90 (84-98)	0.1*
Laboratory tests results at admission			
CRP mg/dl	6.7 (1.4-33.3)	33.4 (5.5-68.2)	0.005*
PCT ng/ml	0.34 (0.13-1.15)	1.25 (0.25-7.55)	0.09*
WBC $10^3/\mu L$	8.82 (6.6-11.54)	6.36 (3.42-8.58)	0.027*
Neutrophils $10^3/\mu L$	4.2 (2.06-7.2)	2.4 (1.2-4.8)	0.11*
Lymphocytes $10^3/\mu L$	1.92 (1.04-4.48)	0.8 (0.4-1.4)	0.002*
PLT $10^3/\mu L$	243 (158-335)	133 (8-207)	<0.001*
LDH U/L	287.5 (253-412)	478.7 (347.5-1210.7)	0.11*
CK U/L	89 (52-121)	66 (66-66)	0.65*
Ferritin µg/L	238.5 (112.9-450)	507 (193.8-1101.7)	0.29*
ALT U/L	25 (14-47)	24 (19.5-63)	0.45*
Management and outcome			

Oxygen therapy (days)	5 (2-7)	21 (7-29)	<0.001*
Mechanical ventilation (days)		21 (4-29)	n.a.
Remdesivir therapy (n/%)	24 (45)	6 (35)	0.58**
Remdesivir – onset date (days after admission)	5 (3-8)	2 (2-2)	0.015*
Length of stay (days)	9 (6-11)	29 (10-37)	<0.001*
PICU admission (n%)	11 (21)	16 (94)	<0.001**
Death (n/%)	0	8 (47)	<0.001**

* - p value for Kruskall-Wallis test

** – p value for chi-square test.

Children who required mechanical ventilation during COVID-19 were characterized by a higher incidence of chronic diseases (94 vs. 53%; p=0.003). These children reported slightly earlier after the onset of the first symptoms (3 vs. 4 days). On admission, they manifested less frequent cough (35 vs. 81%; p<0.001) and dehydration (19 vs. 59%; p=0.01). The markers of inflammation were higher (median CRP 33.4 vs. 6.7 mg/dl; p=0.005), and lymphopenia and thrombocytopenia were observed. Moreover, higher concentrations of ferritin and LDH were found. It can be seen, that 45% and 35% of children in both groups respectively (p-value-0.58), have been treated with remdesivir, so the difference is not statistically significant. Medium length of stay was longer in the group of mechanically ventilated patients (29 vs 9 days), as was the length of oxygen therapy (21 vs 5 days). 11 (21%) children with noninvasive oxygen support and 16 (94%) in the group with invasive mechanical ventilation were treated in PICU (p <0.001). 8 children requiring mechanical ventilation died during hospitalization and 9 recovered. The most significant difference between children who recovered, and those who died was age – 124 versus 12.8 months.

Risk factors for death in children with severe COVID-19

Table 2 presents a comparison of data in groups of children with severe COVID-19 who survived, and those who died during severe COVID-19. The children who died because of COVID-19 were in our special interest. They all presented underlying chronic diseases (100 vs 57%) and reported slightly earlier from the onset of the first symptoms (3 vs. 4 days). On admission, they presented a less frequent cough (25 vs. 76%; p=0.007) and normal SatO2 (96 vs. 88%; p=0.002). It is worth noting, that the markers of inflammation were higher (median CRP 55.9 vs. 7.9 mg/dL; p=0.02), and deep lymphopenia (0.65 vs 1.85 $10^3/\mu L$, p=0.005), and thrombocytopenia (7 vs 237 $10^3/\mu L$, p<0.001) were observed. Significant differences in ferritin (252.1 vs 1521.5 µg/l, p<001) and LDH (1210.7 vs 287.5 U/L, p =0.028) levels were found. The time of hospitalization was much shorter in the group of survivors (9 vs 26 days). All eight fatalities were the result of COVID-19. All children had underlying diseases but they were in stable condition when contracted COVID-19. The clinical manifestation of the disease leading to death was also typical for COVID-19, not for underlying diseases.

Table II. Characteristics of patients with severe course of COVID-19, who recovered and who died.

	Survivors of severe COVID-19 (n=62)	Children who died during severe COVID-19 (n=8)	p-value
Demographic data			
Age (months) - Me; (IQR)	35.1 (9.4-168)	12.8 (5.1-31.8)	0.05*
Sex (male/female)	28/34	3/5	0.784**
Chronic illness (n/%)	35 (57)	8 (100)	0.02**
Clinical data at admission			
Day from the onset of symptoms (days)	4 (2-6)	3 (1-3)	0.079*
Fever (n/%)	44 (71)	3 (38)	0.16**
Cough (n/%)	47 (76)	2 (25)	0.007**
Dyspnoe (n/%)	59 (95)	6 (75)	0.1**

Dehydration (n/%)	31 (51)	3 (38)	0.78**
Neurologic symptoms (n/%)	27 (44)	4 (50)	1.0**
SpO2 at admission (%)	88 (84-90)	96 (92-100)	0.002*
Laboratory tests results at admission			
CRP mg/dL	7.9 (2.4-38.1)	55.9 (5.9-232.6)	0.02*
PCT ng/ml	0.4 (0.14-2.17)	1.25 (0.25-142.3)	0.34*
WBC $10^3/\mu L$	8.56 (6.1-11.4)	7.03 (1.39-9.54)	0.09*
Neutrophils $10^3/\mu L$	3.7 (2.12-6.62)	2.75 (0.5-5.8)	0.2*
Lymphocytes $10^3/\mu L$	1.85 (0.9-4.42)	0.65 (0.2-0.9)	0.005*
PLT $10^3/\mu L$	237 (156-306)	7 (5-35)	<0.001*
LDH U/L	287.5 (252-422.5)	1210.7 (347.5-4701)	0.028*
ALT U/L	24.5 (15-46.5)	25 (22-65)	0.28*
Management and outcome			
Remdesivir therapy (n/%)	28 (45)	2 (25)	0.45**
Remdesivir – onset date (days after admission)	4 (2-7)	3 (2-3)	0.46*
Length of stay (days)	9 (7-13)	26 (8-49)	0.05*

* - p value for Kruskall-Wallis test

** – p value for chi-square test.

Risk factors for severe course of COVID-19 in children

A comparison of selected demographic, clinical, and laboratory factors is presented in Table III.

The patients with severe COVID-19 were older (median age 34.8 vs 18.5 months, p=0.008). On admission, they more often presented cough (81% versus 54%, p<0.001) so as dyspnoea (78% versus 10%, p<0.001), and auscultation changes (77.8% versus 18.8%, p<0.001).

What is interesting, underlying chronic diseases were only slightly more frequent in the group of severely ill children (39% versus 25%, p= 0.08). Only immunosuppression was much more common

in the group with the severe course (8.3% versus 1.3%, p <0.001). Laboratory tests' results were similar in both groups, only little differences in platelet count and D-dimers on admission were found.

It is worth noting that there is a significant difference between the studied groups in BCG vaccination (97% among the patients with mild course and only 88% in the group with severe course, p=0.002).

Table III. Characteristics of patients with severe and non-severe COVID-19.

	Severe COVID-19 (n=36)	Non-severe COVID-19 (n=1371)	p-value
Demographic data			
Age (months) - Me; (IQR)	34.8 (10.3-175)	18.5 (5.6-62.6)	0.008*
Sex (male/%)	14 (39)	728 (53)	0.09**
Chronic illness (n/%)	14 (39)	343 (25)	0.08**
Immunocompromised (n/%)	3 (8.3)	18 (1.3)	0.015**
BCG vaccination (n/%)	30 (88)	1286 (97)	0.016**
Clinical data at admission			
Day from the onset of symptoms (days)	4 (2-7)	2 (1-5)	0.006*
Fever (n/%)	27 (75)	955 (70)	0.58**
Cough (n/%)	29 (81)	741 (54)	0.002**
Dyspnoe (n/%)	28 (78)	139 (10)	<0.001**
GI disturbances (n/%)	6 (18)	231 (17)	0.81**
Smell disturbances (n/%)	2 (5.6)	73 (5.3)	0.72**
Taste disturbances (n/%)	2 (5.6)	72 (5.3)	0.71**
Neurologic symptoms (n/%)	4 (11)	129 (9.4)	0.77**
Laboratory tests results at admission			
CRP mg/dL	3 (1-29,3)	2.9 (1-11)	0.42*
WBC $10^3/\mu L$	8.75 (6.3-12)	7.9 (5.8-11.2)	0.54*

Neutrophils $10^3/\mu L$	3.16 (1.54-8.06)	2.65 (1.53-4.65)	0.09*
Lymphocytes $10^3/\mu L$	3.76 (1.26-5.53)	3.41 (1.95-5.5)	0.26*
PLT $10^3/\mu L$	232 (157-357)	288 (222-360)	0.04*
LDH U/L	272 (220-401)	278 (229-319)	0.45*
ALT U/L	20 (13-33)	20 (14-39)	0.76*
D-dimer ng/mL	543 (329-982)	921 (489-1568)	0.01*
Outcome			
Length of stay (days)	9 (6-11)	3 (2-5)	<0.001*

* - p value for Kruskall-Wallis test

** – p value for chi-square test.

Discussion

During 3 years of the COVID-19 pandemic, the course of the disease has been changing. It was due to the following SARS-CoV-2 variants and raising herd immunity. Since the beginning of the pandemic children have been considered to have a good prognosis. Now the number of cases is small and the course of COVID-19 is usually mild but hospitalization among children has increased since the emergence of contagious SARS-CoV-2 variants and the achievement of a high vaccination rate in adults. The severity prediction is still important to help medical decision-making.

As a first step, the definition of severity should be described. There is no consensus definition of pediatric severe COVID-19 and in previous studies, different definitions were used. The most popular is the WHO definition in which severe course can be diagnosed in a child with clinical signs of pneumonia (cough or difficulty in breathing + fast breathing or chest wall indrawing + at least one of the following: SpO2 < 90%; Very severe chest wall indrawing, grunting, central cyanosis, or presence of any other general danger sign (inability to breastfeed or drink, lethargy or unconsciousness, or convulsions)) [12]. While the diagnosis can be made on clinical grounds; chest imaging (radiograph, computed tomography (CT) scan, ultrasound) may assist in diagnosis and identify or exclude pulmonary complications [13].

Other investigators expressed their own definitions. Zachariah et al. [14] defined severity as the need for ventilatory or hemodynamic support, and Dong et al. [15] defined it as having respiratory symptoms, dyspnea, and hypoxemia. Armin et al. [16] have included a set of events that present the severity of COVID-19 disease: using a ventilator, oxygen with reservoir, taking a vasoactive drug, intravenous immunoglobulin (IVIG) or corticosteroid therapy, and death.

In this study, we used severity classification for acute SARS-CoV-2 infection provided in the multicenter interim guidance on the use of antivirals for children with COVID-19 [6], [7]. This was because they met the requirements for the use of antivirals in children and allowed for MIS-C exclusion.

The characteristic of our patients with the severe course was similar to those in other studies, but the significant difference was the frequency of comorbidities which were only slightly more common in patients with the severe course. Other authors described the overwhelming prevalence of patients with comorbidities [17-19]. It might have been due to the different definitions of disease severity in other studies.

Nevertheless in our cohort in the group of patients requiring invasive oxygen treatment the prevalence of those with underlying conditions was significant, and 100% of children who died because of COVID-19 had comorbidities. The most often were the same as in other studies - genetic conditions, neurologic conditions, metabolic conditions, cardiovascular disease, obesity, diabetes mellitus, chronic pulmonary diseases; immunosuppression [20], [21].

All children who died presented underlying diseases – three – cardiological (congenital heart defects, cardiomyopathy), two of them were premature, one – Cri du chat syndrome, one- polycystic kidney disease, and one – acute lymphoblastic leukemia (ALL). Among all children with the severe course, there was a significant predominance of those with neurological disorders, development retardation, cardiovascular diseases, genetic disorders, and neonates. 13% of children had multiple comorbidities. It was also found by other authors that having multiple underlying conditions is

associated with an increased risk of severe disease [19], [22]. In multicenter studies of children admitted to PICUs with COVID-19 and COVID-19-related deaths, most of the patients had one or more underlying conditions [20], [23], [24].

Although immune compromise has been reported as an underlying condition in children with severe COVID-19, the relationship between immune compromise and severe COVID-19 has not been well established. In small surveys of children who developed COVID-19 while receiving immunosuppressive medications COVID-19 was mild [25], [26]. In another study that included eight children with rheumatic disease, active disease, and use of glucocorticoids were associated with severe disease [5], [27]. In our study immunosuppression was significantly more common in the group of children with severe course of the disease.

Childhood cancer appears to be associated with increased severity of COVID-19. In a global registry study of COVID-19 in children with cancer including 1500 patients, severe or critical infection, and mortality was higher than that in the general pediatric population [5], [28]. Among children with cancer, the severe disease has been associated with intensive chemotherapy, neutropenia, lymphopenia, comorbidity, and coinfection [28], [29]. There was only one child with ALL among children with severe COVID-19 in our cohort. Children with hematologic malignancy do not appear to be at greater risk of severe COVID-19 than children with nonhematologic malignancy [5], [30].

Other conditions that may be associated with severe disease in children, but for which the evidence is inconsistent, include age <1 year [19], [24], [31], [32], Down syndrome [33], [34] and prematurity [35], [36]. Our study confirmed them as a risk factor for severe pediatric COVID-19.

In our cohort children who required mechanical ventilation manifested cough and dehydration more often, contrary to cases described in other studies. Also, similar laboratory results of higher markers of inflammation, lymphopenia, and thrombocytopenia with higher concentrations of ferritin and LDH are reported by other authors [16], [18]. In children who died because of COVID-

19 inflammation markers, leucopenia, thrombocytopenia, LDH, and ferritin level were extremely high (Table II).

In this study, the BCG vaccination was also considered to be a factor that influenced COVID-19 severity, because it was hypothesized that countries without widespread tuberculosis prevention policies had a higher percentage of severe cases (Italy, France, and Spain) than countries that adopted long-term widespread prevention (Japan, Denmark, and Korea). In Poland, antituberculosis BCG vaccination was obligatory, so in our pediatric study groups, over 95% of patients had been vaccinated. The lack of BCG vaccination was found in 12% of children with severe COVID-19 and 3 % in other hospitalized children. Various publications have described the results of the first association between BCG vaccination and COVID-19 case severity, but these have concerned only adults [37].

Our study had several limitations. The recommendations regarding the rules for COVID-19 testing, indications for hospitalization, and treatment availability were changing during the pandemic. This could have influenced the number of hospitalized and treated children. So did the length of hospitalization.

Almost all children taking part in our study were Caucasian. In Poland, ethnical diversity is at low level; racial minorities are very small. In other reports, Black African and Hispanic populations were significantly overrepresented among severe COVID-19 paediatric cases.

The next limitation is a relatively small number of patients with severe course of COVID-19 in our study. Moreover, it can't be ruled out that a child with severe disease could have been hospitalised and even could have died in another hospital in our region. Also, a lot of definitions of COVID-19's severity makes the comparison with other studies difficult.

Conclusions

In our study risk factors for a severe course of COVID-19 were – young age, lack of COVID-19 and BCG vaccination, auscultation changes, and dyspnea on admission. The presence of comorbidities, high

CRP, LDH, and ferritin levels were the predictors of mechanical ventilation necessity and death. Among children mechanically ventilated teenagers were the patients with a prognosis of recovery but, infants with comorbidities were at the highest risk of death. Our observations may be useful for defining the high-risk group for severe COVID-19 and could help to guide hospital admission and prevention of COVID-19 in paediatric patients.

Acknowledgments: There was no grant support made available for this research.

Conflict of interest: The authors declare no conflict of interest.

References

1. O'Driscoll M, Ribeiro Dos Santos G, Wang et al. Age-specific mortality and immunity patterns of SARS-CoV-2. Nature 2021; 590: 140–5.

2. CDC Data. Available from: https://data.cdc.gov/d/9bhg-hcku/visualization. Accessed March 15, 2023.

3. Coronavirus (COVID-19) Latest Insights: Deaths. https://www.ons.gov.uk/peoplepopulationandcommunity/healthandsocialcare/conditionsanddiseases/articles/coronaviruscovid19latestinsights/deaths#deaths-by-age. Accessed March 15, 2023

4. COVID-19: Management in children. Available from: https://www.uptodate.com/contents/covid-19-management-in-children?topicRef=127488&source=see_link. Accessed March 15, 2023.

5. Demographic Trends of COVID-19 cases and deaths in the US reported to CDC. Available from: https://covid.cdc.gov/covid-data-tracker/#demographics. Accessed March 15, 2023.

6. COVID-19: Clinical manifestations and diagnosis in children. Available from: https://www.uptodate.com/contents/covid-19-management-in-children?topicRef=127488&source=see_link. Accessed March 15, 2023.

7. Chiotos K, Hayes M, Kimberlin DW et al. Multicenter Interim Guidance on Use of Antivirals for Children With Coronavirus Disease 2019/Severe Acute Respiratory Syndrome Coronavirus 2. J Pediatric Infect Dis Soc 2021; 10: 34–48.

8. WHO Recommendations for national SARS-CoV-2 testing strategies and diagnostic capacities. Available from: https://www.who.int/publications/i/item/WHO-2019-nCoV-lab-testing-2021.1-eng. Accessed March 15, 2023.

9. Polish National Institute of Public Health Recommendations on SARS-Cov2 Laboratory Diagnostics. Available from: https://www.pzh.gov.pl/koronawirus-sars-cov-2/wytyczne-i-rekomendacje/. Accessed March 15, 2023.

10. EMA Summary of Product Characteristics Veklury 100 mg. Available from: https://www.ema.europa.eu/en/documents/other/veklury-product-information-approved-chmp-25-june-2020-pending-endorsement-european-commission_en.pdf. Accessed March 15, 2023.

11. Fact sheet for healthcare providers Emergency Use Authorization (EUA) of Veklury® (remdesivir) for the treatment of coronavirus disease 2019 (Covid-19) in pediatric patients weighing 3.5 kg to less than 40 kg or pediatric patients less than 12 years of age weighing at least 3.5 kg, with positive results of direct Sars-cov-2 viral testing who are: hospitalized, or not hospitalized and have mild-to-moderate Covid-19, and are at high risk for progression to severe Covid-19, including hospitalization or death. Available from: https://www.fda.gov/media/137566/download. Accessed March 15, 2023.

12. National Institutes of Health. Coronavirus Disease 2019 (COVID-19) Treatment Guidelines. Available from: https://www.covid19treatmentguidelines.nih.gov/. Accessed March 15, 2023.

13. WHO Living guidance for clinical management of COVID-19. Available from: https://apps.who.int/iris/bitstream/handle/10665/349321/WHO-2019-nCoV-clinical-2021.2-eng.pdf. Accessed March 15, 2023.

14. Zachariah P, Johnson CL, Halabi KC et al. Epidemiology, Clinical Features, and Disease Severity in Patients With Coronavirus Disease 2019 (COVID-19) in a Children's Hospital in New York City, New York. JAMA Pediatr 2020; 174: e202430.

15. Dong Y, Mo X, Hu Y et al. Epidemiology of COVID-19 Among Children in China. Pediatrics 2020; 145.

16. Armin S, Mirkarimi M, Pourmoghaddas Z et al. Evidence-Based Prediction of COVID-19 Severity in Hospitalized Children. Int J Clin Pract 2022; 2022: 1918177.

17. Choi JH, Choi S-H, Yun KW. Risk Factors for Severe COVID-19 in Children: A Systematic Review and Meta-Analysis. J Korean Med Sci 2022; 37: e35.

18. Kara AA, Böncüoğlu E, Kıymet E et al. Evaluation of predictors of severe-moderate COVID-19 infections at children: A review of 292 children. J Med Virol 2021; 93: 6634–40.

19. Woodruff RC, Campbell AP, Taylor CA et al. Risk Factors for Severe COVID-19 in Children. Pediatrics 2022; 149.

20. Shekerdemian LS, Mahmood NR, Wolfe KK et al. Characteristics and Outcomes of Children With Coronavirus Disease 2019 (COVID-19) Infection Admitted to US and Canadian Pediatric Intensive Care Units. JAMA Pediatr 2020; 174: 868–73.

21. Williams N, Radia T, Harman K, Agrawal P, Cook J, Gupta A. COVID-19 Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection in children and adolescents: a systematic review of critically unwell children and the association with underlying comorbidities. Eur J Pediatr 2021; 180: 689–97.

22. Preston LE, Chevinsky JR, Kompaniyets L, et al. Characteristics and Disease Severity of US Children and Adolescents Diagnosed With COVID-19. JAMA Netw open 2021; 4: e215298.

23. González-Dambrauskas S, Vásquez-Hoyos P, Camporesi A et al. Pediatric Critical Care and COVID-19. Pediatrics 2020; 146.

24. Götzinger F, Santiago-García B, Noguera-Julián A et al. COVID-19 in children and adolescents in Europe: a multinational, multicentre cohort study. Lancet Child Adolesc Heal 2020; 4: 653–61.

25. Marlais M, Wlodkowski T, Vivarelli M et al. The severity of COVID-19 in children on immunosuppressive medication. Lancet Child Adolesc Health 2020; 4: e17-e18.

26. Sengler C, Eulert S, Minden K et al. Clinical manifestations and outcome of SARS-CoV-2 infections in children and adolescents with rheumatic musculoskeletal diseases: data from the National Paediatric Rheumatology Database in Germany. RMD open 2021; 7.

27. Calvo C, Udaondo C. COVID-19 in Children With Rheumatic Diseases in the Spanish National Cohort EPICO-AEP. J Rheumatol. 2021; 48: 1190-1192.

28. Mukkada S, Bhakta N, Chantada GL et al. Global characteristics and outcomes of SARS-CoV-2 infection in children and adolescents with cancer (GRCCC): a cohort study. Lancet Oncol 2021; 22: 1416–26.

29. Haeusler GM, Ammann RA, Carlesse F et al. SARS-CoV-2 in children with cancer or after haematopoietic stem cell transplant: An analysis of 131 patients. Eur J Cancer 2021; 159: 78–86.

30. Millen GC, Arnold R, Cazier J-B et al. COVID-19 in children with haematological malignancies. Arch Dis Child 2022; 107: 186–8.

31. Parri N, Magistà AM, Marchetti F et al. Characteristic of COVID-19 infection in pediatric patients: early findings from two Italian Pediatric Research Networks. Eur J Pediatr 2020; 179: 1315–23.

32. Ouldali N, Yang DD, Madhi F et al. Factors Associated With Severe SARS-CoV-2 Infection. Pediatrics 2021; 147.

33. Newman AM, Jhaveri R, Patel AB, Tan TQ, Toia JM, Arshad M. Trisomy 21 and Coronavirus Disease 2019 in Pediatric Patients. J Pediatr 2021; 228: 294-296.

34. Ku JH, Levin MJ, Luo Y et al. Risk of Severe Coronavirus Disease 2019 Disease in Individuals With Down Syndrome: A Matched Cohort Study From a Large, Integrated Health Care System. J Infect Dis 2022; 226: 757–65.

35. Kompaniyets L, Agathis NT, Nelson JM et al. Underlying Medical Conditions Associated With Severe COVID-19 Illness Among Children. JAMA Netw open 2021; 4: e2111182.

36. Wallace B, Chang D, Woodworth K et al. Illness severity indicators in newborns by COVID-19 status in the United States, March-December 2020. J Perinatol Off J Calif Perinat Assoc 2022; 42: 446–53.

37. Czajka H, Zapolnik P, Krzych Ł et al. A Multi-Center, Randomised, Double-Blind, Placebo-Controlled Phase III Clinical Trial Evaluating the Impact of BCG Re-Vaccination on the Incidence and Severity of SARS-CoV-2 Infections among Symptomatic Healthcare Professionals during the COVID-19 Pandem. Vaccines 2022; 10.

Decision: **accept without changes**

June 03, 2023
AMS-15487-2023-02
Risk factors of severe course and fatality in children hospitalized for COVID-19 – two centers cohort study.

Dear Dr Lidia Stopyra,

I am pleased to inform you that your manuscript, entitled: Risk factors of severe course and fatality in children hospitalized for COVID-19 – two centers cohort study., has been finally accepted for publication in Archives of Medical Science.

We would like to inform that your paper will be published after receiving publishing fee. In order to receive the invoice, please complete the form including data for invoicing, which is available in the payment bookmark. Failure to complete this form means that you choose not to obtain the invoice.

Please log in to your account:
https://www.editorialsystem.com/ams/article/341615/view/payment/
to proceed with the payment.

If you are paying by wire transfer please indicate manuscript number the name of the contact author and the title. In case of any problems or questions please do not hesitate to contact the technical editor at: eshelp@termedia.pl. We would appreciate if you could confirm payment within 14 days in order to ensure your manuscript to be included in one of the forthcoming issues.

Thank you for submitting your work to our journal.

Kindest regards,
Prof. Maciej Banach, MD, PhD, FAHA, FESC, FNLA
Editor-in-Chief,
Archives of Medical Science
http://www.archivesofmedicalscience.com

Review 1:

I would like to thank the Authors for answering all the queries. I have no further suggestions. In my opinion, the manuscript is suitable for acceptance in the current form. I would like to recommend it for publication.

Review 2:

None

Review 3:

Review
- The Authors have made corrections according to the Reviewer's suggestions.

Section Editor recommendation

Authors have addressed all concerns.

7. OŚWIADCZENIA WSPÓŁAUTORÓW

Kraków, dnia 26 maja 2023 r.

Lek. Aleksandra Kowalik
I Klinika Pediatrii
Uniwersytetu Jagiellońskiego Colegium Medicum.

OŚWIADCZENIE

Jako współautor pracy

Characteristic of Hospitalized Pediatric Patients in the First Five Waves of the COVID-19 pandemic in the Single Center in Poland – 1407 Cases.

opublikowanej *Journal of Clinical Medicine* 2022, Nov; *11*(22), 6806

oświadczam, iż mój własny wkład merytoryczny w przygotowanie, przeprowadzenie i opracowanie badań oraz przedstawienie pracy w formie publikacji polegał na:

- gromadzeniu danych i realizacji badania
- przygotowania manuskryptu do publikacji

Jednocześnie wyrażam zgodę na przedłożenie ww. pracy przez lek. Lidię Stopyrę jako część rozprawy doktorskiej w formie spójnego tematycznie zbioru artykułów opublikowanych w czasopismach naukowych.

Oświadczam, iż samodzielna i możliwa do wyodrębnienia część ww. pracy wykazuje indywidualny wkład lek Lidii Stopyry w **65%** polegający na:

- opracowywaniu pomysłu badań,
- stworzeniu hipotezy badawczej,
- opracowaniu koncepcji badań,
- wykonywaniu części eksperymetalnej
- opracowaniu i interpretacji wyników tej pracy,
- przygotowaniu manuskryptu pracy.

Aleksandra Kowalik

(podpis współautora)

Aleksandra Kowalik
LEKARZ
3482156

Kraków, dnia 26 maja 2023 r.

Lek. Justyna Stala
Oddział Chorób Infekcyjnych i Pediatrii
Szpitala Specjalistycznego im. S. Żeromskiego w Krakowie.

OŚWIADCZENIE

Jako współautor pracy

Characteristic of Hospitalized Pediatric Patients in the First Five Waves of the COVID-19 pandemic in the Single Center in Poland – 1407 Cases.

opublikowanej *Journal of Clinical Medicine* 2022, Nov; *11*(22), 6806

oświadczam, iż mój własny wkład merytoryczny w przygotowanie, przeprowadzenie i opracowanie badań oraz przedstawienie pracy w formie publikacji polegał na:
- gromadzeniu danych i realizacji badania.

Jednocześnie wyrażam zgodę na przedłożenie ww. pracy przez lek. Lidię Stopyrę jako część rozprawy doktorskiej w formie spójnego tematycznie zbioru artykułów opublikowanych w czasopismach naukowych.

Oświadczam, iż samodzielna i możliwa do wyodrębnienia część ww. pracy wykazuje indywidualny wkład lek Lidii Stopyry w **65%** polegający na:

- opracowywaniu pomysłu badań,
- stworzeniu hipotezy badawczej,
- opracowaniu koncepcji badań,
- wykonywaniu części eksperymetalnej
- opracowaniu i interpretacji wyników tej pracy, przygotowaniu manuskryptu pracy.

Justyna Stala
LEKARZ
3653868

.....
(podpis współautora)

Kraków, dnia 26 maja 2023 r.

Lek. Justyna Szebla
Oddział Chorób Infekcyjnych i Pediatrii
Szpitala Specjalistycznego im. S. Żeromskiego w Krakowie.

OŚWIADCZENIE

Jako współautor pracy

Characteristic of Hospitalized Pediatric Patients in the First Five Waves of the COVID-19 pandemic in the Single Center in Poland – 1407 Cases.

opublikowanej *Journal of Clinical Medicine* 2022, Nov; *11*(22), 6806

oświadczam, iż mój własny wkład merytoryczny w przygotowanie, przeprowadzenie i opracowanie badań oraz przedstawienie pracy w formie publikacji polegał na:
- gromadzeniu danych i realizacji badania.

Jednocześnie wyrażam zgodę na przedłożenie ww. pracy przez lek. Lidię Stopyrę jako część rozprawy doktorskiej w formie spójnego tematycznie zbioru artykułów opublikowanych w czasopismach naukowych.

Oświadczam, iż samodzielna i możliwa do wyodrębnienia część ww. pracy wykazuje indywidualny wkład lek Lidii Stopyry w **65%** polegający na:

- opracowywaniu pomysłu badań,
- stworzeniu hipotezy badawczej,
- opracowaniu koncepcji badań,
- wykonywaniu części eksperymetalnej
- opracowaniu i interpretacji wyników tej pracy, przygotowaniu manuskryptu pracy.

Justyna Szebla

(podpis współautora)

Justyna Szebla
LEKARZ
3601249

Kraków, dnia 26 maja 2023 r.

Lek. Ida Majchrzak
Oddział Chorób Infekcyjnych i Pediatrii
Szpitala Specjalistycznego im. S. Żeromskiego w Krakowie.

OŚWIADCZENIE

Jako współautor pracy

Characteristic of Hospitalized Pediatric Patients in the First Five Waves of the COVID-19 pandemic in the Single Center in Poland – 1407 Cases.

opublikowanej w *Journal of Clinical Medicine*. **2022**, *11*(22), 6806;

oświadczam, iż mój własny wkład merytoryczny w przygotowanie, przeprowadzenie i opracowanie badań oraz przedstawienie pracy w formie publikacji polegał na:
- gromadzeniu danych i realizacji badania.

Jednocześnie wyrażam zgodę na przedłożenie ww. pracy przez lek .Lidię Stopyrę jako część rozprawy doktorskiej w formie spójnego tematycznie zbioru artykułów opublikowanych w czasopismach naukowych.

Oświadczam, iż samodzielna i możliwa do wyodrębnienia część ww. pracy wykazuje indywidualny wkład lek Lidii Stopyry w **65%** polegający na:

- opracowywaniu pomysłu badań,
- stworzeniu hipotezy badawczej,
- opracowaniu koncepcji badań,
- wykonywaniu części eksperymetalnej
- opracowaniu i interpretacji wyników tej pracy, przygotowaniu manuskryptu pracy.

Ida Majchrzak
LEKARZ
3136206

Ida Majchrzak
.....
(podpis współautora)

Kraków, dnia 26 maja 2023 r.

Lek. Mateusz Jakosz
Oddział Chorób Infekcyjnych i Pediatrii
Szpitala Specjalistycznego im. S. Żeromskiego w Krakowie.

OŚWIADCZENIE

Jako współautor pracy

Characteristic of Hospitalized Pediatric Patients in the First Five Waves of the COVID-19 pandemic in the Single Center in Poland – 1407 Cases.

opublikowanej *Journal of Clinical Medicine* 2022, Nov; *11*(22), 6806

oświadczam, iż mój własny wkład merytoryczny w przygotowanie, przeprowadzenie i opracowanie badań oraz przedstawienie pracy w formie publikacji polegał na:
- gromadzeniu danych i realizacji badania.

Jednocześnie wyrażam zgodę na przedłożenie ww. pracy przez lek. Lidię Stopyrę jako część rozprawy doktorskiej w formie spójnego tematycznie zbioru artykułów opublikowanych w czasopismach naukowych.

Oświadczam, iż samodzielna i możliwa do wyodrębnienia część ww. pracy wykazuje indywidualny wkład lek Lidii Stopyry w **65%** polegający na:

- opracowywaniu pomysłu badań,
- stworzeniu hipotezy badawczej,
- opracowaniu koncepcji badań,
- wykonywaniu części eksperymetalnej
- opracowaniu i interpretacji wyników tej pracy, przygotowaniu manuskryptu pracy.

Mateusz Jakosz
lekarz
3655709
Mateusz Jakosz
(podpis współautora)

Kraków, dnia 26 maja 2023 r.

Lek. Karolina Grzywaczewska
Oddział Chorób Infekcyjnych i Pediatrii
Szpitala Specjalistycznego im. S. Żeromskiego w Krakowie.

OŚWIADCZENIE

Jako współautor pracy

Characteristic of Hospitalized Pediatric Patients in the First Five Waves of the COVID-19 pandemic in the Single Center in Poland – 1407 Cases.

opublikowanej *Journal of Clinical Medicine* 2022, Nov; *11*(22), 6806

oświadczam, iż mój własny wkład merytoryczny w przygotowanie, przeprowadzenie i opracowanie badań oraz przedstawienie pracy w formie publikacji polegał na:
- gromadzeniu danych i realizacji badania.

Jednocześnie wyrażam zgodę na przedłożenie ww. pracy przez lek. Lidię Stopyrę jako część rozprawy doktorskiej w formie spójnego tematycznie zbioru artykułów opublikowanych w czasopismach naukowych.

Oświadczam, iż samodzielna i możliwa do wyodrębnienia część ww. pracy wykazuje indywidualny wkład lek Lidii Stopyry w **65%** polegający na:

- opracowywaniu pomysłu badań,
- stworzeniu hipotezy badawczej,
- opracowaniu koncepcji badań,
- wykonywaniu części eksperymetalnej
- opracowaniu i interpretacji wyników tej pracy, przygotowaniu manuskryptu pracy.

Karolina Grzywaczewska
LEKARZ
3583365

.....
(podpis współautora)

Kraków, dnia 26 maja 2023 r.

Prof.dr hab. Przemko Kwinta
I Klinika Pediatrii
Uniwersytetu Jagiellońskiego Colegium Medicum.

OŚWIADCZENIE

Jako współautor pracy

Characteristic of Hospitalized Pediatric Patients in the First Five Waves of the COVID-19 pandemic in the Single Center in Poland – 1407 Cases.

opublikowanej *Journal of Clinical Medicine* 2022, Nov; *11*(22), 6806

oświadczam, iż mój własny wkład merytoryczny w przygotowanie, przeprowadzenie i opracowanie badań oraz przedstawienie pracy w formie publikacji polegał na:

- opracowaniu koncepcji badań
- opracowaniu i interpretacji wyników pracy.
- przygotowaniu manuskryptu pracy

Jednocześnie wyrażam zgodę na przedłożenie ww. pracy przez lek .Lidię Stopyrę jako część rozprawy doktorskiej w formie spójnego tematycznie zbioru artykułów opublikowanych w czasopismach naukowych.

Oświadczam, iż samodzielna i możliwa do wyodrębnienia część ww. pracy wykazuje indywidualny wkład lek Lidii Stopyry w **65%** polegający na:

- opracowywaniu pomysłu badań,
- stworzeniu hipotezy badawczej,
- opracowaniu koncepcji badań,
- wykonywaniu części eksperymetalnej
- opracowaniu i interpretacji wyników tej pracy,
- przygotowaniu manuskryptu pracy.

.....
(podpis współautora)

Kraków, dnia 26 maja 2023 r.

Lek. Aleksandra Kowalik
I Klinika Pediatrii
Uniwersytetu Jagiellońskiego Colegium Medicum.

OŚWIADCZENIE

Jako współautor pracy

The Age-Related Course of COVID-19 in Pediatric Patients—1405 Cases in a Single Center.

opublikowanej w *Journal of Clinical Medicine.* **2022**, Dec; 11(24): 7347

oświadczam, iż mój własny wkład merytoryczny w przygotowanie, przeprowadzenie i opracowanie badań oraz przedstawienie pracy w formie publikacji polegał na:

- gromadzeniu danych i realizacji badania.
- Przygotowaniu manuskryptu do publikacji.

Jednocześnie wyrażam zgodę na przedłożenie ww. pracy przez lek .Lidię Stopyrę jako część rozprawy doktorskiej w formie spójnego tematycznie zbioru artykułów opublikowanych w czasopismach naukowych.

Oświadczam, iż samodzielna i możliwa do wyodrębnienia część ww. pracy wykazuje indywidualny wkład lek Lidii Stopyry w **70%** polegający na:

- opracowywaniu pomysłu badań,
- stworzeniu hipotezy badawczej,
- opracowaniu koncepcji badań,
- wykonywaniu części eksperymetalnej
- opracowaniu i interpretacji wyników tej pracy, przygotowaniu manuskryptu pracy.

Aleksandra Kowalik
(podpis współautora)

Aleksandra Kowalik
LEKARZ
3482156

Kraków, dnia 26 maja 2023 r.

Lek. Justyna Stala
Oddział Chorób Infekcyjnych i Pediatrii
Szpitala Specjalistycznego im. S. Żeromskiego w Krakowie.

OŚWIADCZENIE

Jako współautor pracy

The Age-Related Course of COVID-19 in Pediatric Patients—1405 Cases in a Single Center.

opublikowanej w *Journal of Clinical Medicine.* **2022**, Dec; 11(24): 7347

oświadczam, iż mój własny wkład merytoryczny w przygotowanie, przeprowadzenie i opracowanie badań oraz przedstawienie pracy w formie publikacji polegał na:
- gromadzeniu danych i realizacji badania.

Jednocześnie wyrażam zgodę na przedłożenie ww. pracy przez lek .Lidię Stopyrę jako część rozprawy doktorskiej w formie spójnego tematycznie zbioru artykułów opublikowanych w czasopismach naukowych.

Oświadczam, iż samodzielna i możliwa do wyodrębnienia część ww. pracy wykazuje indywidualny wkład lek Lidii Stopyry w **70%** polegający na:

- opracowywaniu pomysłu badań,
- stworzeniu hipotezy badawczej,
- opracowaniu koncepcji badań,
- wykonywaniu części eksperymetalnej
- opracowaniu i interpretacji wyników tej pracy, przygotowaniu manuskryptu pracy.

Justyna Stala
LEKARZ
3653868

Justyna Stala

.....

(podpis współautora)

Kraków, dnia 26 maja 2023 r.

Lek. Ida Majchrzak
Oddział Chorób Infekcyjnych i Pediatrii
Szpitala Specjalistycznego im. S. Żeromskiego w Krakowie.

OŚWIADCZENIE

Jako współautor pracy

The Age-Related Course of COVID-19 in Pediatric Patients—1405 Cases in a Single Center.

opublikowanej w *Journal of Clinical Medicine*. **2022**, Dec; 11(24): 7347

oświadczam, iż mój własny wkład merytoryczny w przygotowanie, przeprowadzenie i opracowanie badań oraz przedstawienie pracy w formie publikacji polegał na:
- gromadzeniu danych i realizacji badania.

Jednocześnie wyrażam zgodę na przedłożenie ww. pracy przez lek .Lidię Stopyrę jako część rozprawy doktorskiej w formie spójnego tematycznie zbioru artykułów opublikowanych w czasopismach naukowych.

Oświadczam, iż samodzielna i możliwa do wyodrębnienia część ww. pracy wykazuje indywidualny wkład lek Lidii Stopyry w **70%** polegający na:

- opracowywaniu pomysłu badań,
- stworzeniu hipotezy badawczej,
- opracowaniu koncepcji badań,
- wykonywaniu części eksperymetalnej
- opracowaniu i interpretacji wyników tej pracy, przygotowaniu manuskryptu pracy.

Ida Majchrzak
LEKARZ
3136206

.....
(podpis współautora)

Kraków, dnia 26 maja 2023 r.

Lek. Mateusz Jakosz
Oddział Chorób Infekcyjnych i Pediatrii
Szpitala Specjalistycznego im. S. Żeromskiego w Krakowie.

OŚWIADCZENIE

Jako współautor pracy

The Age-Related Course of COVID-19 in Pediatric Patients—1405 Cases in a Single Center.

opublikowanej w *Journal of Clinical Medicine.* **2022**, Dec; 11(24): 7347

oświadczam, iż mój własny wkład merytoryczny w przygotowanie, przeprowadzenie i opracowanie badań oraz przedstawienie pracy w formie publikacji polegał na:
- gromadzeniu danych i realizacji badania.

Jednocześnie wyrażam zgodę na przedłożenie ww. pracy przez lek .Lidię Stopyrę jako część rozprawy doktorskiej w formie spójnego tematycznie zbioru artykułów opublikowanych w czasopismach naukowych.

Oświadczam, iż samodzielna i możliwa do wyodrębnienia część ww. pracy wykazuje indywidualny wkład lek Lidii Stopyry w **70%** polegający na:

- opracowywaniu pomysłu badań,
- stworzeniu hipotezy badawczej,
- opracowaniu koncepcji badań,
- wykonywaniu części eksperymetalnej
- opracowaniu i interpretacji wyników tej pracy, przygotowaniu manuskryptu pracy.

Mateusz Jakosz
lekarz
3655709

Mateusz Jakosz .....

(podpis współautora)

Kraków, dnia 26 maja 2023 r.

Lek. Justyna Szebla
Oddział Chorób Infekcyjnych i Pediatrii
Szpitala Specjalistycznego im. S. Żeromskiego w Krakowie.

OŚWIADCZENIE

Jako współautor pracy

The Age-Related Course of COVID-19 in Pediatric Patients—1405 Cases in a Single Center.

opublikowanej w *Journal of Clinical Medicine*. **2022**, Dec; 11(24): 7347

oświadczam, iż mój własny wkład merytoryczny w przygotowanie, przeprowadzenie i opracowanie badań oraz przedstawienie pracy w formie publikacji polegał na:
- gromadzeniu danych i realizacji badania.

Jednocześnie wyrażam zgodę na przedłożenie ww. pracy przez lek .Lidię Stopyrę jako część rozprawy doktorskiej w formie spójnego tematycznie zbioru artykułów opublikowanych w czasopismach naukowych.

Oświadczam, iż samodzielna i możliwa do wyodrębnienia część ww. pracy wykazuje indywidualny wkład lek Lidii Stopyry w **70%** polegający na:

- opracowywaniu pomysłu badań,
- stworzeniu hipotezy badawczej,
- opracowaniu koncepcji badań,
- wykonywaniu części eksperymetalnej
- opracowaniu i interpretacji wyników tej pracy, przygotowaniu manuskryptu pracy.

Justyna Szebla

.....
(podpis współautora)

Justyna Szebla
LEKARZ
3901249

Kraków, dnia 26 maja 2023 r.

Prof.dr hab. Przemko Kwinta
I Klinika Pediatrii
Uniwersytetu Jagiellońskiego Colegium Medicum.

OŚWIADCZENIE

Jako współautor pracy

The Age-Related Course of COVID-19 in Pediatric Patients—1405 Cases in a Single Center.

opublikowanej w *Journal of Clinical Medicine*. **2022**, Dec; 11(24): 7347

oświadczam, iż mój własny wkład merytoryczny w przygotowanie, przeprowadzenie i opracowanie badań oraz przedstawienie pracy w formie publikacji polegał na:

- opracowaniu koncepcji badań
- opracowaniu i interpretacji wyników pracy.
- przygotowaniu manuskryptu pracy

Jednocześnie wyrażam zgodę na przedłożenie ww. pracy przez lek .Lidię Stopyrę jako część rozprawy doktorskiej w formie spójnego tematycznie zbioru artykułów opublikowanych w czasopismach naukowych.

Oświadczam, iż samodzielna i możliwa do wyodrębnienia część ww. pracy wykazuje indywidualny wkład lek Lidii Stopyry w **70%** polegający na:

- opracowywaniu pomysłu badań,
- stworzeniu hipotezy badawczej,
- opracowaniu koncepcji badań,
- wykonywaniu części eksperymetalnej
- opracowaniu i interpretacji wyników tej pracy,
- przygotowaniu manuskryptu pracy.

.....
(podpis współautora)

Kraków, dnia 3 czerwca 2023r.

Lek. Łukasz Wentrys
Oddział Chorób Infekcyjnych i Pediatrii
Szpital Specjalistyczny im. S. Żeromskiego w Krakowie

OŚWIADCZENIE

Jako współautor pracy pt

Risk factors of severe course and fatality in children hospitalized for COVID-19 – two centers cohort study.

Opublikowanej w *Archives of Medical Science 2023,*

oświadczam, iż mój własny wkład merytoryczny w przygotowanie, przeprowadzenie i opracowanie badań oraz przedstawienie pracy w formie publikacji polegał na
- gromadzenie danych i realizacja badania

Jednocześnie wyrażam zgodę na przedłożenie ww. pracy przez lek. Lidię Stopyrę jako część rozprawy doktorskiej w formie spójnego tematycznie zbioru artykułów opublikowanych w czasopismach naukowych.

Oświadczam, iż samodzielna i możliwa do wyodrębnienia część ww. pracy wykazuje indywidualny wkład lek. Lidii Stopyry w **75%** polegający na:
- opracowywaniu pomysłu badań
- stworzeniu hipotezy badawczej
- opracowywaniu koncepcji badań
- wykonywaniu części eksperymentalnej
- opracowaniu i interpretacji wyników
- przygotowaniu manuskryptu pracy

lek. Łukasz Wentrys
3652473

.....
(podpis współautora)

Kraków, dnia 3 czerwca 2023r.

Prof.dr hab. Przemko Kwinta
I Klinika Pediatrii
Uniwersytetu Jagiellońskiego Collegium Medicum

OŚWIADCZENIE

Jako współautor pracy pt

Risk factors of severe course and fatality in children hospitalized for COVID-19 – two centers cohort study.

Opublikowanej w *Archives of Medical Science 2023.*

oświadczam, iż mój własny wkład merytoryczny w przygotowanie, przeprowadzenie i opracowanie badań oraz przedstawienie pracy w formie publikacji polegał na

- opracowaniu koncepcji badan
- stworzeniu hipotezy badawczej
- opracowaniu i interpretacji wyników
- przygotowaniu manuskryptu pracy

Jednocześnie wyrażam zgodę na przedłożenie ww. pracy przez lek. Lidię Stopyrę jako część rozprawy doktorskiej w formie spójnego tematycznie zbioru artykułów opublikowanych w czasopismach naukowych.

Oświadczam, iż samodzielna i możliwa do wyodrębnienia część ww. pracy wykazuje indywidualny wkład lek. Lidii Stopyry w **75%** polegający na:

- opracowywaniu pomysłu badań
- stworzeniu hipotezy badawczej
- opracowywaniu koncepcji badań
- wykonywaniu części eksperymentalnej
- opracowaniu i interpretacji wyników
- przygotowaniu manuskryptu pracy

.....
(podpis współautora)

Kraków, dnia 3 czerwca 2023r.

Lek. Aleksandra Kowalik
I Klinika Pediatrii
Uniwersytetu Jagiellońskiego Collegium Medicum

OŚWIADCZENIE

Jako współautor pracy pt

Risk factors of severe course and fatality in children hospitalized for COVID-19 – two centers cohort study.

Opublikowanej w *Archives of Medical Science 2023,*

oświadczam, iż mój własny wkład merytoryczny w przygotowanie, przeprowadzenie i opracowanie badań oraz przedstawienie pracy w formie publikacji polegał na

- gromadzenie danych i realizacja badania
- przygotowaniu manuskryptu do publikacji

Jednocześnie wyrażam zgodę na przedłożenie ww. pracy przez lek. Lidię Stopyrę jako część rozprawy doktorskiej w formie spójnego tematycznie zbioru artykułów opublikowanych w czasopismach naukowych.

Oświadczam, iż samodzielna i możliwa do wyodrębnienia część ww. pracy wykazuje indywidualny wkład lek. Lidii Stopyry w **75%** polegający na:

- opracowywaniu pomysłu badań
- stworzeniu hipotezy badawczej
- opracowywaniu koncepcji badań
- wykonywaniu części eksperymentalnej
- opracowaniu i interpretacji wyników
- przygotowaniu manuskryptu pracy

Aleksandra Kowalik
(podpis współautora)

Aleksandra Kowalik
LEKARZ
3482156