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Epidemiology of 7375 children and adolescents hospitalized with COVID-19 in Germany, reported via a prospective, nationwide surveillance study in 2020–2022

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By means of a nationwide, prospective, multicenter, observational cohort registry collecting data on 7375 patients with laboratory-confirmed SARS-CoV-2 admitted to children's hospitals in Germany, March 2020–November 2022, our study assessed the clinical features of children and adolescents hospitalized due to SARS-CoV-2, evaluated which of these patients might be at highest risk for severe COVID-19, and identified underlying risk factors. Outcomes tracked included: symptomatic infection, case fatality, sequelae at discharge and severe disease. Among reported cases, median age was one year, with 42% being infants. Half were admitted for reasons other than SARS-CoV-2. In 27%, preexisting comorbidities were present, most frequently obesity, neurological/neuromuscular disorders, premature birth, and respiratory, cardiovascular or gastrointestinal diseases. 3.0% of cases were admitted to ICU, but ICU admission rates varied as different SARS-CoV-2 variants gained prevalence. Main risk factors linked to ICU admission due to COVID-19 were: patient age (> 12 and 1–4 years old), obesity, neurological/neuromuscular diseases, Trisomy 21 or other genetic syndromes, and coinfections at time of hospitalization. With Omicron, the group at highest risk shifted to 1–4-year-olds. For both health care providers and the general public, understanding risk factors for severe disease is critical to informing decisions about risk-reduction measures, including vaccination and masking guidelines.

Abbreviations

CI	Confidence interval
COVID-19	Coronavirus disease 2019
CPAP	Continuous positive airway pressure

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CW	Calendar week
DGPI	German Society for Pediatric Infectious Diseases
ECMO	Extracorporeal membrane oxygenation
ENT	Ear, nose and throat
h/o	History of
ICU	Intensive care unit
IQR	Interquartile range
pARDS	Pediatric acute respiratory distress syndrome
PID	Primary immunodeficiency
REDCap	Research electronic data capture
RKI	Robert Koch-Institute, Berlin, Germany
RF	Risk factor
RR	Relative risk
SARS-CoV-2	Severe acute respiratory syndrome coronavirus type 2
SIRS	Systemic inflammatory response syndrome
s/p	Status post
TU Dresden	Technische Universität Dresden
VOC	Variant of concern

With its start in December 2019, COVID-19 rapidly emerged as a global pandemic. Although early monitoring indicated that clinical severity and hospitalization rates among children with SARS-CoV-2 were lower than among adults[1], concrete data supporting such observations had yet to be collected.

With the aim of better understanding which children might be at highest risk for severe COVID-19 disease and of identifying underlying risk factors[2], the German Society for Pediatric Infectious Diseases (DGPI) launched a nationwide survey to collect data on children and adolescents with laboratory-confirmed SARS-CoV-2 infections who had been admitted to pediatric hospitals in Germany between January 2020 and November 2022. For both health care providers and the general public, being able to better identify risk factors for severe disease would be critical to informing decisions about, and the implementation of, risk-reduction measures, including vaccination and masking guidelines.

Objective

Our study's goal was to analyze the clinical characteristics, disease course and outcome predictors from prospectively-documented pediatric patients. In addition, we aimed to examine shifts related to the emergence of different dominant variants of SARS-CoV-2 (VOC) during the course of the pandemic.

Methods

On March 18, 2020, our group established a prospective, multicenter, observational cohort registry to collect data on children and adolescents hospitalized with SARS-CoV-2 infections in Germany. Austrian hospitals also were invited to participate.

Settings and case definitions

Eligible for inclusion in the study were pediatric patients with a laboratory-confirmed (real-time reverse transcriptase polymerase chain reaction and/or rapid antigen test) SARS-CoV-2 infection who had been hospitalized between January 1, 2020 to November 30, 2022, (with retrospective case recording allowed for the period January 1, 2020 to March 18, 2020). Cases of Pediatric Inflammatory Multisystem Syndrome (PIMS), also known as Multisystem Inflammatory Syndrome in Children (MIS-C), were documented in a separate DGPI register.

For each patient, an electronic case report form was completed with an access point via the DGPI website[3] that linked to a REDCap-based survey[4,5] hosted at Technische Universität Dresden.

Information collected via predefined data fields included: demographic characteristics, exposure, comorbidities, initial symptoms, clinical signs, medical treatment (including antiviral therapy), disease course during hospitalization, and outcome at discharge. SARS-CoV-2-related symptoms and therapy were documented by the reporting physician according to his/her individual assessment of the patient. SARS-CoV-2-directed therapies were defined as those provided to a patient for the purpose of treating his/her SARS-CoV-2 infection or COVID-19 disease, but not for any other medical reasons. Antiviral therapy was defined as use of an agent with a direct antiviral activity against SARS-CoV-2.

Weekly data reports were made publicly accessible via the DGPI website[3].

Age groups

Following the age-group designations outlined by the official COVID-19 vaccination guidelines for children in Germany, age groups were defined as: "under 1 year old", "1–4 years old", "5–11 years old" and "12–17 years old".

Comorbidities

Evaluated as potential risk factors (RF) for severe COVID-19 disease course were: respiratory, cardiovascular, gastrointestinal, hepatic, renal, neurological/neuromuscular, psychiatric, hematological, and oncological comorbidities, as well as autoimmune, syndromic diseases, obesity, primary immunodeficiency (PID), s/p transplant (solid organ, stem cell or bone marrow), history of prematurity, tracheostomy, at-home oxygen therapy administered prior to SARS-CoV-2 infection, and coinfections.

Outcome measures

The main outcome categories were: symptomatic infection, case fatality, persistent symptoms/sequelae at discharge, and severe disease, as defined by the need for ICU treatment due to COVID-19 disease.

Definition of variants of concern (VOC)

In Germany, monitoring of SARS-CoV-2 variants is managed by the Robert Koch Institute (RKI), which also makes such data publicly available. On the basis of this RKI data, we outlined six phases during which different variants of concern predominated (Fig. 1B). The dominant variant was defined as that which accounted for > 50% of the SARS-CoV-2 infections in Germany during any given calendar week[6].

Statistical analysis

Analysis was performed using R v.3.6.3 and Microsoft Excel v.2010. Graphics were created using Datawrapper software (datawrapper.de) and R. Descriptive statistics were presented as medians, with first and third quartiles for continuous variables, and absolute frequencies with percentages shown for categorical variables. Using robust Poisson regression, we evaluated the relative risk (RR) for development of severe disease by examining ICU cases according to age, comorbidities and other RF. Only symptomatic patients (N = 6512 out of 7375 patients total) were included for the assessment of RF for severe disease. In addition, predefined disease groups, (ones with an occurrence of $n \geq 6$), were analyzed by a bivariate model in order to evaluate the relative risk for ICU admission. P-values were calculated using Chi-Square and U-Tests. We quantified the precision of RR estimates by 95% confidence intervals (CI) and applied a significance level of 0.05 in order to test two-sided hypotheses.

Ethics approval

The DGPI registry and its protocol was approved by the Ethics Committee of the Technische Universität Dresden (BO-EK-110032020) and was assigned clinical trial number DRKS00021506 in the German clinical trials register[7]. All methods were carried out in accordance with relevant guidelines and regulations. Due to anonymized data collection, informed consent from the patients and/or their legal guardians was not necessary according to our local Ethics Committee.

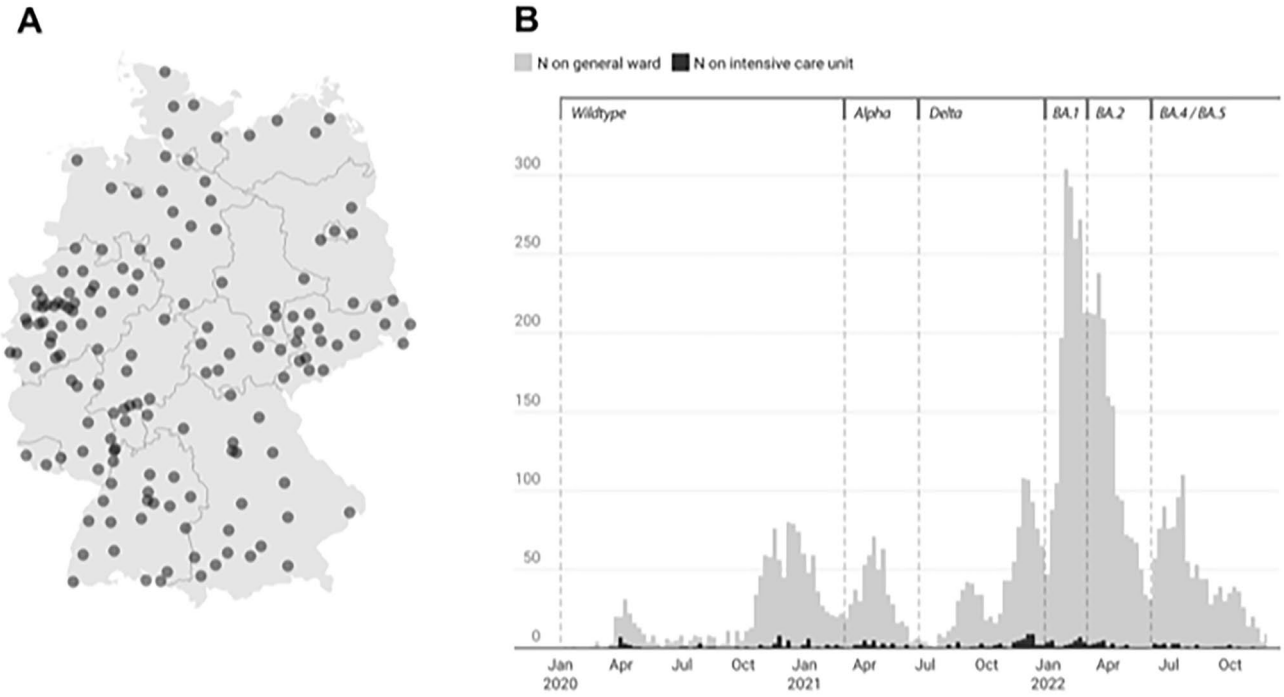

Figure 1. (**A**) Pediatric hospitals in Germany submitting cases of patients hospitalized with COVID-19 to the registry, January 1, 2020–November 30, 2022 (n = 198; DGPI COVID-19 working group). (**B**) Pediatric cases on general wards and intensive care units, as reported to the COVID-19 Survey, January 1, 2020–November 30, 2022. The relative predominance of different SARS-CoV-2 variants of concern (VOC) in Germany since the beginning of the COVID-19 pandemic has been determined according to VOC data provided by the Robert Koch-Institute (RKI)[6]. According to calendar week (CW), these phases were: Wildtype (CW 1, 2020–CW 8, 2021); Alpha VOC (CW 9–24, 2021); Delta VOC (CW 25–51, 2021; Omicron BA.1 VOC (CW 52, 2021–CW 8, 2022); Omicron BA.2 VOC (CW 9–22, 2022); and Omicron BA.4/BA.5 VOC (CW 23–48, 2022).

Ethical approval

The registry was approved by the Ethics Committee of the Technische Universität Dresden (BO-EK-110032020) and was assigned clinical trial number DRKS00021506 (https://drks.de/search/en/trial/DRKS00021506).

Results

Demographics and clinical characteristics

Overall, 7375 hospitalized children and adolescents with a laboratory-confirmed SARS-CoV-2 infection were reported to the registry from January 1, 2020 to November 30, 2022. Of these, 7341 were hospitalized in Germany, where 59.3% (198/334) of all children's hospitals reported cases and all 16 federal states were represented (Fig. 1A). An additional 34 patients were reported from two hospitals in Austria.

Among reported cases, median age of patients was one year old (IQR, 0–9), with 41.9% (n = 3093) being infants < 1 year old (Table 1). Of these, 9.1% (n = 281) were born prematurely, with a median gestational age of 34 weeks (range 23–37). There was no significant gender predominance (53.7% male).

The impact of SARS-CoV-2 on different age groups varied and also shifted along with the emergence of different VOCs over time. Among infants, COVID-19-related hospitalizations increased significantly ($p < 0.001$) as the pandemic progressed, with notable jumps occurring between the wildtype (37.4%, n = 444 of 1186), Delta (42.1%, n = 408 of 968), and Omicron BA.4/5 phases (50.1%, n = 589 of 1176). At the same time, hospitalization rates for adolescents decreased significantly ($p = 0.0001$) between the wildtype (26.6%, n = 315 of 1186) and Omicron BA.4/5 phases (8.9%, n = 105 of 1176) (Fig. 2A).

Roughly half of the 7375 cases submitted to the registry—54.2% of all cases (n = 3995) and 45.9% of patients under one year old (n = 3094)—were hospitalized for reasons other than a SARS-CoV-2 infection.

Among hospitalized patients, 74.8% (n = 5518) were reported to have SARS-CoV-2-related symptoms during hospital stay (Table 1). Fever was the most frequently-reported symptom, followed by respiratory, ear, nose and throat (ENT) and gastrointestinal symptoms. Upper respiratory tract infections were the most common diagnosis at time of hospital discharge, followed by lower respiratory tract infections, including bronchitis/bronchiolitis, pneumonia (X-ray/CT-confirmed) and pediatric acute respiratory distress syndrome (pARDS) (Table 1, Fig. 2B).

As successive SARS-CoV-2 variants emerged, the spectrum of discharge diagnoses changed. During the pandemic's early phase, asymptomatic SARS-CoV-2 infections were reported at higher rates than in later periods (18.8% wildtype vs. 8.1% Omicron BA.4/5). With the rise of Alpha, and even more so with Omicron, pseudocroup was more commonly noted, especially among 1–4-year-olds. The number of children and adolescents with pneumonia diagnoses decreased with the arrival of the Omicron variants (7.5% wildtype vs. 2.1% Omicron BA.4/5). The same was true for pARDS (1.6% wildtype vs. 0.3% Omicron BA.4/5). During the wildtype phase, sepsis and SIRS were more frequently noted (2.1%), but once Omicron arrived, this shifted and they became among the rarest diagnoses (0.4–0.6%).

Treatment

Median length of hospitalization reported was three days (IQR 2–6). Overall, only 19.6% (n = 1443/7375) of patients received any SARS-CoV-2-directed therapy (Table 1). The most commonly-reported SARS-CoV-2-related therapies included: general supportive therapy (e.g., antipyretic and fluid therapy), pulmonary support, oxygen supplementation, and invasive or non-invasive respiratory support (e.g., CPAP or high flow oxygen therapy). 78 patients (1.1%) received at least one antiviral drug with anticipated activity against SARS-CoV-2. Additional information regarding types of antivirals prescribed and which patients received antiviral therapy is shown in eTable 1.

Of all cases submitted to the register, 3.0% (n = 223) were admitted to ICU due to COVID-19-related symptoms. Of ICU patients, 85.2% needed respiratory support, including invasive ventilation and extracorporeal membrane oxygenation. Notably, the need for ICU care differed significantly among wildtype-infected patients (4.9%, n = 58/1186) versus those infected with Alpha (5.5%, n = 30/542), Delta (5.3%, n = 51/986) or Omicron (1.5–2.6%, n = 84/4679), ($p < 0.001$ wildtype vs. Omicron) (Fig. 3A).

While hospitalized, all age groups received SARS-CoV-2-related treatment at a similar rate (range 17–22%) (Fig. 3B). However, infants were less likely (p = 0.0001) to be admitted to ICU (1.4%, n = 43) than were adolescents (12–17 years old, 5.6%, n = 73), who had the highest ICU admission rates of all age groups. Infants born prematurely received a higher rate of therapy (25.3%, n = 71) than did mature infants (17.5%, n = 491, p = 0.0012).

Comorbidities

In 27.0% of cases (n = 1993), at least one comorbidity was present. The most common comorbidities were obesity and neurological/neuromuscular disorders, followed by respiratory and cardiovascular disorders (eTable 2).

Outcome and disease severity predictors

For 98.6% of hospitalized patients (n = 7273), overall outcome was favorable (Table 1). Upon discharge, they had either no symptoms or else only mild, residual ones. A small percentage of patients, (0.4%, n = 27), showed irreversible sequelae at time of discharge. In total, 0.4% of patients (n = 33) died at a timepoint that correlated with their SARS-CoV-2 infections. Following the case information submitted by the reporting physicians, 54.5% of these deaths (n = 18) were attributable to COVID-19. Of note, however, 15 of these 18 deceased patients had significant comorbidities and/or complex, chronic conditions, (e.g., cardiovascular, neurological, gastrointestinal, primary immunodeficiency conditions and/or genetic syndromes). Ages of the deceased patients ranged from 6 months to 16 years. Seven of the 15 patients who died were in palliative care for treatment of a pre-existing condition before their SARS-CoV-2 infection occurred. Four additional deaths were due to clearly-defined conditions

	All N = 7375 N (%)		General pediatric ward N = 7152 N (%)		Intensive care unit N = 223 N (%)		*p* value**
Clinical symptoms and complications during hospitalization	5518	74.8	5315	74.3	203	91.0	< 0.001
General Symptoms (including fever), n (%)	4279	58.0	4116	57.6	163	73.1	< 0.001
Fever (> 38.0 °C), n (%)	3796	51.5	3648	51.0	148	66.4	< 0.001
ENT, n (%)	2102	28.5	2047	28.6	55	24.7	0.49
Respiratory, n (%)	2163	29.3	1975	27.6	188	84.3	< 0.001
Cardiovascular, n (%)	253	3.4	198	2.8	55	24.7	< 0.001
Gastrointestinal, n (%)	1297	17.6	1264	17.7	33	14.8	0.2
Hepatic, n (%)	66	0.9	57	0.8	9	4.0	< 0.001
Renal, n (%)	68	0.9	46	0.6	22	9.9	< 0.001
Neurological/Neuromuscular, n (%)	558	7.6	516	7.2	42	18.8	< 0.001
Musculoskeletal, n (%)	137	1.8	128	1.8	9	4.0	< 0.001
Psychiatric, n (%)	31	0.4	28	0.4	3	1.4	0.06
Hematological, n (%)	251	3.4	220	3.1	31	13.9	< 0.001
Autoimmune, n (%)	16	0.2	11	0.2	5	2.2	< 0.001
Other, n (%)	736	10.0	717	10.0	19	8.5	0.42
Discharge diagnosis							
COVID-19 (symptomatic disease), n (%)	5998	81.3	5784	80.9	214	96.0	< 0.001
Asymptomatic SARS-CoV-2 infection, n (%)	863	11.7	862	12.1	1	0.5	< 0.001
Upper respiratory tract infection (including ENT, pseudocroup), n (%)	2171	29.4	2118	29.6	53	23.8	0.2
Pseudocroup / Laryngotracheitis, n (%)	283	3.8	275	3.9	8	3.6	1
Lower respiratory tract infection (including bronchitis, pneumonia, pARDS), n (%)	1119	15.2	952	13.3	167	74.9	< 0.001
Bronchitis / Bronchiolitis, n (%)	809	11.0	781	10.9	28	12.6	< 0.001
Pneumonia, n (%)	355	4.8	209	2.9	146	65.5	< 0.001
pARDS, n (%)	56	0.8	6	0.1	50	22.4	< 0.001
Gastroenteritis, n (%)	605	8.2	596	8.3	9	4.0	0.04
Meningitis, n (%)	10	0.1	9	0.1	1	0.5	0.2
Encephalitis, n (%)	21	0.3	14	0.2	7	3.1	< 0.001
Sepsis/SIRS, n (%)	60	0.8	35	0.5	25	11.2	< 0.001
SARS-CoV-2-associated therapy, n (%)	1443	19.6	1231	17.2	212	95.1	< 0.001
Pulmonary support*, n (%)	635	8.6	445	6.2	190	85.2	< 0.001
Respiratory support, n (%)*	178	2.4	26	0.4	152	68.2	< 0.001
Invasive ventilation, n (%)*	58	0.8	3	0.0	55	24.7	< 0.001
ECMO, n (%)	14	0.2	0	0.0	14	6.3	< 0.001
Catecholamines / Inotropes, n (%)	58	0.8	9	0.1	49	22.0	< 0.001
Immune modulators, n (%)	584	7.9	443	6.2	141	63.2	< 0.001
Antibiotics, n (%)	403	5.5	253	3.5	150	67.3	< 0.001
Antiviral treatment, n (%)	80	1.1	35	0.5	45	20.2	< 0.001
Outcome at discharge							
No/mild residual symptoms, n (%)	7273	98.6	7088	99.1	185	83.0	< 0.001
Sequelae, n (%)	27	0.4	14	0.2	13	5.8	< 0.001
Death, n (%)	33	0.5	13	0.2	20	9.0	< 0.001
Death due to COVID-19, n (%)	18	0.2	5	0.1	13	5.8	< 0.001

Table 1. General characteristics of children and adolescents hospitalized with laboratory-confirmed SARS-CoV-2 infections, with data compared according to admission to general pediatric wards vs. intensive care units. *Pulmonary support: top-level category includes oxygen supplementation, bronchodilatation, respiratory support (invasive or non-invasive ventilation, such as high-flow oxygen therapy or CPAP) and ECMO. **Statistical analysis was performed with the Chi-Square-Test.

unrelated to SARS-CoV-2. In another four, cause of death could not be determined by the reporting physician. The number of COVID-19-related deaths did not statistically vary during the different VOC periods (eFigure 1).

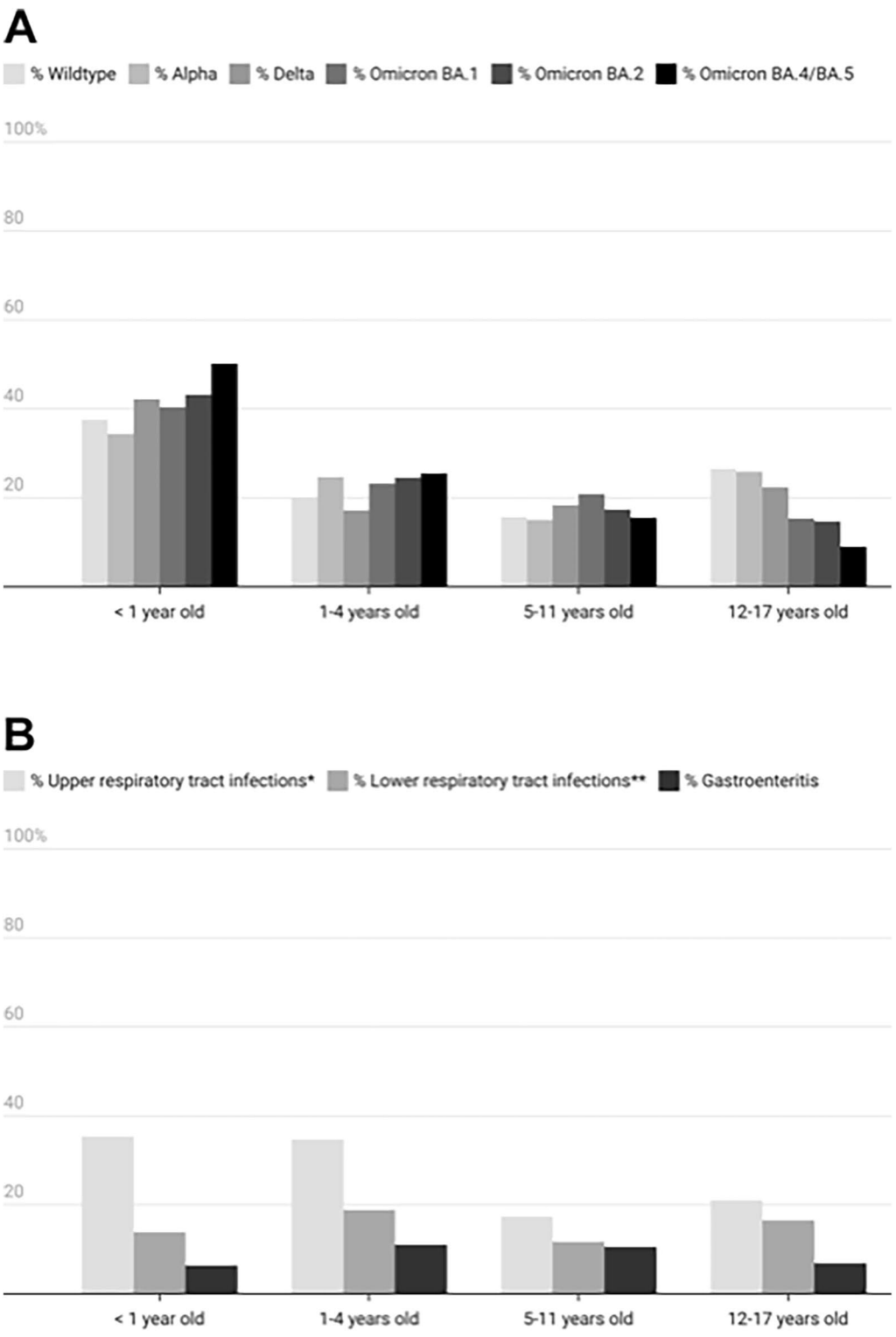

Figure 2. (**A**) Distribution of SARS-CoV-2 variants according to patient age. Pediatric cases reported from January 1, 2020–November 30, 2022. The relative predominance of different SARS-CoV-2 variants of concern (VOC) in Germany since the beginning of the COVID-19 pandemic has been determined according to VOC data provided by the Robert Koch-Institute (RKI)[6]. (**B**) Diagnosis of syndromic conditions among pediatric COVID-19 patients by age. Pediatric cases reported from January 1, 2020–November 30, 2022. *Upper respiratory tract infections included ear, nose and throat infections, as well as pseudocroup. **Lower respiratory tract infections included bronchitis/bronchiolitis, pneumonia and Pediatric Acute Respiratory Syndrome (pARDS).

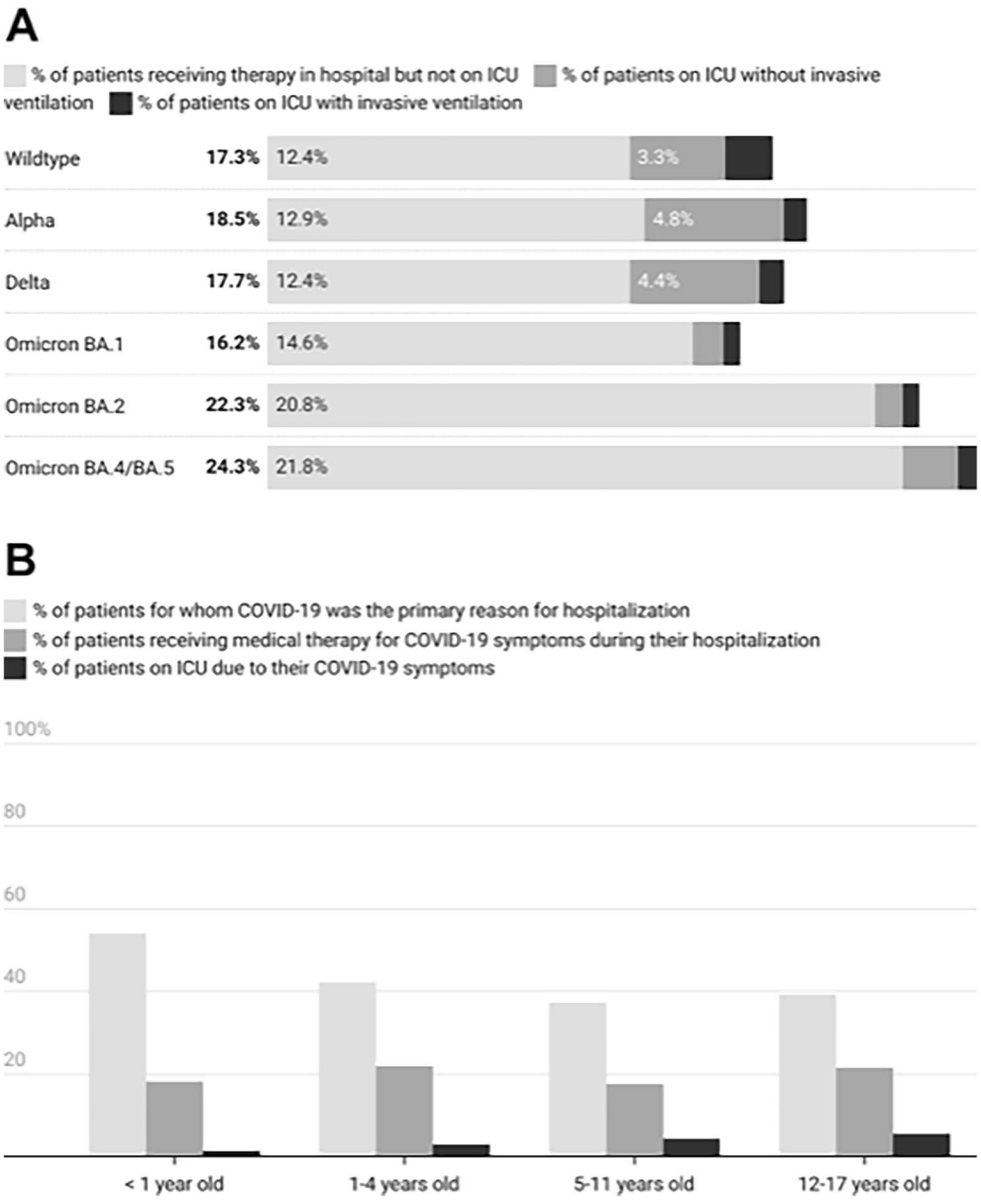

Figure 3. (**A**) Therapy provided in connection with infection from different SARS-CoV-2 variants. Pediatric cases reported from January 1, 2020–November 30, 2022. The relative predominance of different SARS-CoV-2 variants of concern (VOC) in Germany since the beginning of the COVID-19 pandemic has been determined according to VOC data provided by the Robert Koch-Institute (RKI)[6]. (**B**) COVID-19 therapy provided, by age group. Pediatric cases reported from January 1, 2020–November 30, 2022.

Risk assessment for ICU admission

Robust Poisson regression was used to model relationships between RF and ICU admission. Only symptomatic patients were included in this model. In the fully-adjusted model, patient age, obesity, neurological/neuromuscular comorbidities, Trisomy 21, other genetic syndromes, prior at-home oxygen therapy, premature birth and coinfections all were significantly associated with ICU admission (eTable 2, Fig. 4).

Infants were less severely affected. For them, the estimated RR for ICU admission was 150% lower than for 1–4-year-old children, and 200% lower than for those over 11. Trisomy 21 represented a 2.7-fold higher risk of ICU admission than for those without the condition, while coinfection constituted a 2.6-fold higher risk. Types of coinfection are described in eTable 3.

To calculate RR for ICU admission during the pre-Omicron vs. Omicron phases, a robust Poisson regression with two corresponding subsets was used (Fig. 4). This showed that during the pre-Omicron phases, the most significant RFs included: 5–17-year-olds, renal diseases, neurological/neuromuscular diseases, obesity, Trisomy 21 and coinfections. With the emergence of Omicron, the most important RFs became: 1–4-year-olds, neurological/neuromuscular diseases, other genetic syndromes, prior at-home oxygen therapy and coinfections. During their hospital stay, 9.1% of patients (n = 674) experienced coinfections.

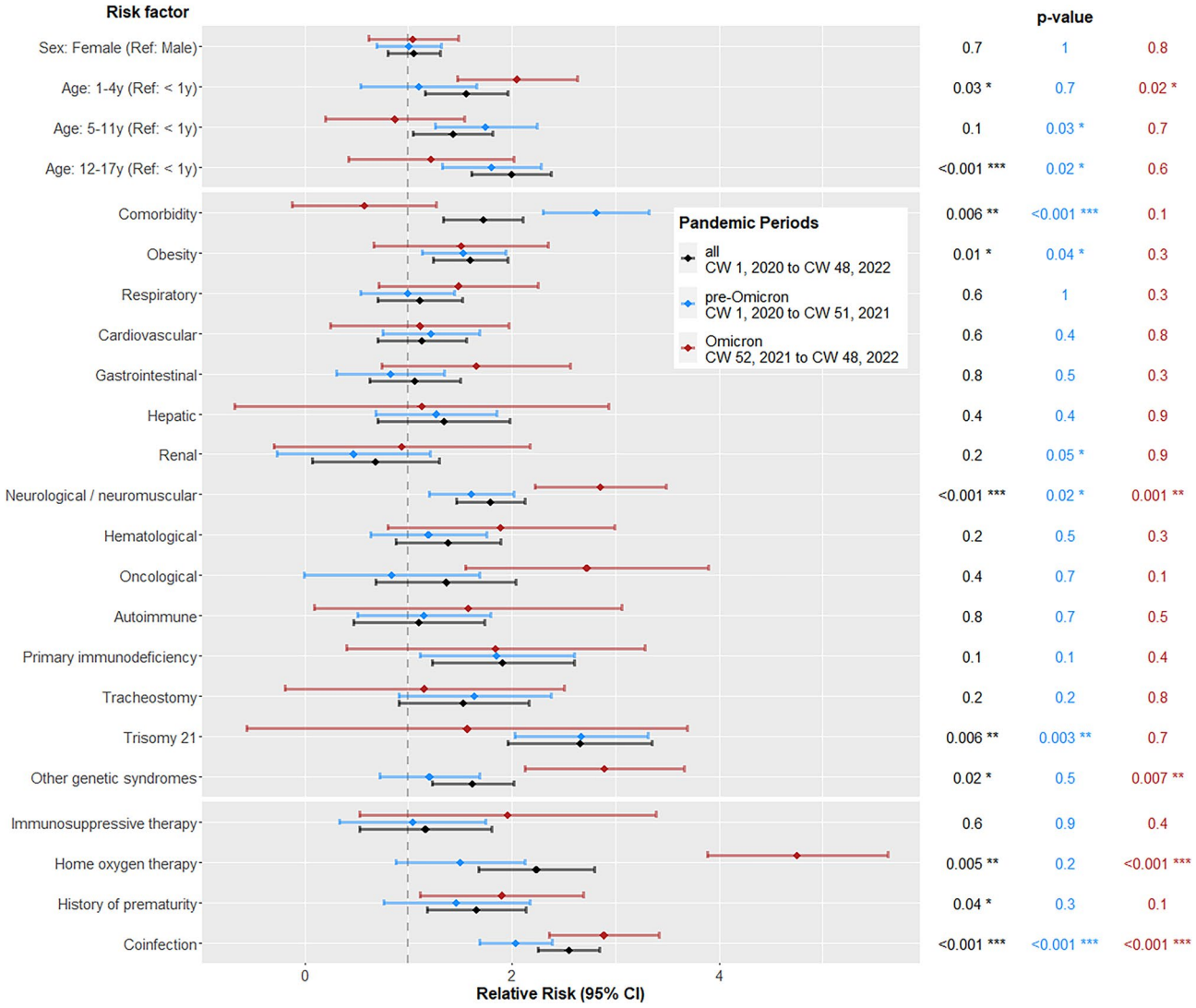

Figure 4. Risk factors for ICU admission; Comparison of three subsets: all patients (CW 1, 2020 to CW 48, 2022), pre-Omicron (CW 1, 2020 to CW 51, 2021) and Omicron (CW 52, 2021 to CW 48, 2022). Only symptomatic patients were included (N = 6512 out of 7375 total). To test a two-sided hypothesis, variables were analyzed in a fully-adjusted Poisson regression model with a 95% confidence interval (CI) and significance level of 0.05.

Bivariate analysis of comorbidities specified as RF for ICU admission, (only counting those with an occurrence among $n \geq 6$ patients on ICU), identified the following comorbidities to be statistically significant: recurrent obstructive bronchitis, pulmonary hypertension, cyanotic and acyanotic heart disease, s/p cardiac surgery, arterial hypertension, heart failure, congenital kidney disease, epilepsy, psychomotor retardation and diabetes mellitus (all types) (eTable 4). Due to the low number of sequelae and reported deaths, predictors of these outcomes were unable to be calculated.

Discussion

Our data corroborate the conclusions of previous studies showing SARS-CoV-2 infections in children usually to be mild—and specifically, that such infections are associated with lower hospitalization and ICU admission rates as compared to SARS-CoV-2 infections among adults[8]. Of note, over half of cases reported were not admitted to hospitals as a direct result of a SARS-CoV-2 infection, but rather for other medical reasons. In these instances, the SARS-CoV-2 infection may be an incidental finding, despite the fact that most of these patients did subsequently develop clinical signs of COVID-19 during their hospital stays. Only 20% of patients received any kind of SARS-CoV-2-related therapy. This reinforces the observation that COVID-19 symptoms generally are mild for the majority of children, even for those who become hospitalized[9,10]. The systematic review by He et al. reported that 16.4–42.7% of children hospitalized with SARS-CoV-2 during the wildtype period were asymptomatic – this as compared to 10.1–23.0% of adults[11]. With the successive emergence of different VOCs during the course of the pandemic, hospitalization and ICU admission rates shifted. Although the highest absolute numbers of COVID-19 admissions occurred during Omicron, overall hospitalization and ICU admission

rates for the general pediatric population simultaneously decreased during this period[11–15]. In the United States, 97.8% of pediatric COVID-19 cases were mild during Omicron, as compared to 84.2% of cases during Delta[15]. Omicron's milder cases generally were attributed to the variant's lower virulence, overall higher vaccinations rates as compared to earlier VOC phases, and the development of higher rates of infection-acquired immunity[14].

Infant hospitalization rates peaked during Omicron. By contrast, other age groups saw hospitalization rates decrease during Omicron as compared to earlier VOC phases. This observation echoes findings from a Detroit-based US study[16], where the proportion of hospitalized infants increased, while the proportion of hospitalized teenagers decreased. Despite Omicron cases having the highest admission frequency, severe illness with Omicron was lower than with either Delta or Alpha. Presumably, this was due to Omicron's high contagiousness, along with its high incidence in the general population—a combination that also led to more cases among infants. Notably, the median age in our cohort was 1 year, with half of them being infants < 3 months old. This rate of affected infants that was higher than that shown by other cohorts[16,17]. Although infants were hospitalized at higher rates than older children relative to their share in the general population[17–19], only 18% of infants required a SARS-CoV-2-related therapy—a level comparable to that for older age groups. From this, however, it should not be concluded that infants are more likely to experience severe courses of disease, as many infant-age admissions are likely to have been due to the taking of precautionary measures, rather than to actual SARS-CoV-2 disease severity.

ICU admission was used as a surrogate parameter for disease severity[20]. More specific outcome predictors—such as mechanical ventilation and use of vasoactive agents—were subsumed under the category of ICU admission (see Table 1). As these predictors applied to under 1% of all patients in our cohort, a more in-depth analysis with statistically-significant results was not possible. Several comorbidities were able to be significantly associated with the need for ICU admission. Specifically, patient age of > 12 years, obesity, Trisomy 21, other genetic syndromes, neurological/neuromuscular diseases and coinfections were shown to be significant risk factors for ICU admission. One international registry reported older patient age and seizure disorders as representing significant RF[8]. In our cohort by contrast, pediatric patients with severe immunosuppression, (e.g., caused by cancer chemotherapy), showed no elevated risk for severe COVID-19. In our analysis of the Omicron phase, only neurological/neuromuscular diseases, genetic syndromes and coinfections remained significant RF for severe outcomes. Obesity and Trisomy 21, detected as significant RF in the pre-Omicron phase, lost their significance with Omicron. In our overall cohort, the relative risk (RR) for ICU admission was highest among 12-to-17-year-olds, followed by 1-to-4-year-olds. During Omicron, the 1-to-4-year-old group maintained an increased RR (Fig. 4). Bhalala et al. showed that for every one-year increase in age, there was a parallel increase in the odds of ICU admission during wildtype phase[8]. With Omicron, however, Butt et al. reported an increased risk for severe disease among patients < 6 years old as compared to those 6–17 years old[12]. COVID-19 vaccinations (especially among high-risk > 5-years-olds), combined with naturally-acquired immunity (heightened due to Omicron's broad scope) also may have contributed to a decreased risk for hospitalization and ICU admission among children > 5 years old[10].

In our bivariate model, patients with recurrent obstructive bronchitis, pulmonary hypertension, cyanotic and acyanotic heart disease, s/p cardiac surgery, arterial hypertension, heart failure, epilepsy, psychomotor retardation, congenital kidney diseases and diabetes mellitus (of any type) all had a significantly higher RR (eTable 4). Consequently, our data suggests that children belonging to these risk groups, and/or who have these specific comorbidities, also may be at higher risk for severe COVID-19 disease. This finding should be taken into consideration when evaluating treatment and protection measures and is particularly relevant for children and adolescents who present with multiple risk factors[21].

Limitations

Given the high participation rates the registry received, (59% of all German pediatric hospitals), along with its especially extensive dataset, (7375 children and adolescents hospitalized with SARS-CoV-2-infection), the DGPI registry is noteworthy as one of the largest prospective, documented case series of hospitalized pediatric COVID-19 cases globally. By capturing detailed information on clinical manifestations, demographic factors and predictors of disease severity, the data collected were comprehensive and robust. Because the registry was conducted in a high-resource country, it most likely will be applicable to other countries with similar medical and socioeconomic environments. However, only a subset of all pediatric SARS-CoV-2 hospitalizations in Germany was reported to the DGPI register. One main limitation of our study therefore lies in a potential selection bias. In addition, over time, asymptomatic or mild COVID-19 cases may have become reported less frequently than at the beginning of the study period. For this reason, we cannot exclude our cohort's potentially underrepresenting severe COVID-19-related disease courses and complications during the later pandemic phases, including Omicron. Consequently, our analysis may overestimate the relative risk for ICU admission. In addition, the overall low case numbers of pediatric patients treated on ICU pose a challenge for reliable analysis, especially with respect to defining single comorbidities and/or specific outcome predictors. Lastly, because patient follow-up ended at the time of hospital discharge, our detection of long-term sequelae is impaired.

Conclusion

In contrast to COVID-19 hospitalization rates for adults in Germany[22], only a small proportion of children and adolescents was hospitalized in direct connection with a SARS-CoV-2 infection. Indeed, over half of the patients in our cohort was admitted for reasons other than a SARS-CoV-2 infection. However, this does not diminish the importance of effort to identify key risk factors that may lead to severe disease, including but not limited to ICU treatment among children with COVID-19. Our study reveals the primary risk factors to be: patients > 11 and < 5 years old, obesity, neurological/neuromuscular diseases, Trisomy 21, other genetic

syndromes and coinfections at time of hospitalization. When Omicron emerged, the age group at highest risk for ICU admission shifted to those < 5 years old.

Data availability

Upon reasonable request, the datasets generated during and/or analyzed as part of the current study are available from the corresponding author.

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Author contributions

All authors contributed to either the conception and design of the study, acquisition of data, or data analysis and interpretation. J.A., M.H., J.H., A.S. and R.B. designed and established the registry. M.D. and N.D. managed the database and validated the data. DT.S., J.B. and A.T. coordinated resources. M.D. analyzed the registry data. M.D. and M.H. wrote the original draft of the manuscript. N.D., J.A., T.T. and R.B. reviewed and edited the manuscript. All authors provided critical revisions and final approval for the decision to submit for publication.

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Competing interests
The authors declare no competing interests.

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