



## Original Research



# Risk factors for intensive care admission in childhood patients with COVID-19 - Results of the German nationwide inpatient sample

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## ABSTRACT

**Background:** COVID-19 pandemic research efforts have mainly focused on adults, but data in paediatric populations are sparse.

**Methods:** We used the German nationwide-inpatient-sample analysing all hospitalized children  $\leq 18$  years with confirmed COVID-19-diagnosis in Germany during the year 2020, stratified for intensive care unit (ICU) admission.

**Results:** Overall, 3360 hospitalization-cases of children  $\leq 18$  years with COVID-19-infection were diagnosed in Germany 2020 (median age 7.0 [IQR 0.0–15.0] years, 49.8 % female); among them 4.3 % were admitted on an ICU. In-hospital death occurred in five patients with and three without ICU admission (3.5 % vs. 0.1 %,  $P < 0.001$ ) and ICU admission was independently associated with increased case-fatality (OR 21.573 [95%CI 4.191–111.044],  $P < 0.001$ ).

Obesity (OR 3.419 [95%CI 1.300–8.993],  $P = 0.013$ ), diabetes mellitus (OR 6.929 [95%CI 3.327–14.432],  $P < 0.001$ ), pneumonia (OR 7.373 [95%CI 4.823–11.271],  $P < 0.001$ ), acute respiratory distress syndrome (ARDS) (OR 48.058 [95%CI 11.689–197.588],  $P < 0.001$ ) and multisystem inflammatory syndrome caused by COVID-19 (OR 9.573 [95%CI 3.036–30.191],  $P < 0.001$ ), heart failure (OR 64.509 [95%CI 24.462–170.121],  $P < 0.001$ ), myocarditis (OR 4.682 [95%CI 1.278–17.149],  $P = 0.020$ ), acute and/or chronic kidney failure (OR 7.946 [95%CI 3.606–17.508],  $P < 0.001$ ), cancer (OR 5.220 [95%CI 2.599–10.485],  $P < 0.001$ ) and liver diseases (OR 5.501 [95%CI 2.177–13.899],  $P < 0.001$ ) were associated with an ICU admission.

**Conclusion:** Proportion of hospitalized paediatric COVID-19-patients admitted on ICU in Germany was low with 4.3 % accompanied by 3.5 % case-fatality rate. Independent factors for ICU admission comprised cardio-vascular risk factors, comorbidities, and complications of COVID-19.

## 1. Introduction

More than three years ago, in December 2019, the first patient-cases of pneumonia caused by an unknown virus were detected in Wuhan,

China [1–3], and on January 5th, 2020, the Department of Zoonoses of the National Institute of Communicable Disease Control and Prevention (Chinese Center for Disease Control and Prevention) announced the identification of a new Coronavirus responsible for a wave of respiratory

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illnesses [4]. From this day on, severe acute respiratory syndrome coronavirus type 2 (SARS-CoV-2) spread throughout the world at an enormous pace, igniting the twenty-first century's deadliest pandemic [2,4]. On January 30th, the WHO declared COVID-19 as a Public Health Emergency of International Concern [4]. First infection cases in Germany were reported at the end of January 2020 in the federal state of Bavaria [2]. The sustained transmission of SARS-CoV-2 also resulted in Germany in a strong spread of COVID-19 in the population [2]. COVID-19 deaths worldwide were estimated as 18.2 million (95 % uncertainty interval 17.1–19.6) people (as measured by excess mortality) between 2020 and 2021 [5]. The global all-ages rate of excess mortality driven by the COVID-19 pandemic was 120.3 deaths (113.1–129.3) per 100,000 population [5]. In the year 2023, the pandemic was still far from being at its end (as hoped by many and announced by President Biden for the United States in September 2022) [4].

Although children and young people aged  $\leq 18$  years represent approximately 2%–5% of the SARS-CoV-2 cases globally, research efforts regarding coronavirus disease 2019 (COVID-19) pandemic have mainly focused on disease course of adults [2,6,7]. It is well known that COVID-19 might cause injuries of the heart, the kidneys, and liver, besides the lungs as primary target organ [2,7–9]. These complications of COVID-19 may in addition with other risk factors trigger adverse outcome in children infected by SARS-CoV-2.

However, data regarding spectrum of illness and risk factors for adverse outcome in pediatric populations are sparse [6,10–12]. Thus, we aimed to close this gap with identification of associated factors with aggravated COVID-19 disease course concomitantly with pediatric intensive care unit (ICU) admissions in Germany.

## 2. Methods

### 2.1. Data source

The statistics of this study were carried out on our behalf by the Research Data Center (RDC) of the Federal Bureau of Statistics (Wiesbaden, Germany) analysing the nationwide inpatient sample (NIS) of Germany (source: RDC of the Federal Statistical Office and the Statistical Offices of the federal states, DRG Statistics 2020, own calculations) [2]. The RDC provided the aggregated statistical results to us, which were computed based on our generated and supplied SPSS code syntax (IBM Corp. Released 2011. IBM SPSS Statistics for Windows, Version 20.0. IBM Corp: Armonk, NY, USA).

The primary aim of the present data analysis of the German NIS, was to identify temporal trends of hospitalized children (aged  $\leq 18$  years, termed as children in the further manuscript) with a confirmed COVID-19 diagnosis (ICD-code U07.1) admitted to the ICU during the observation period between January 1st and December 31st, 2020 and to identify independent predictors of ICU admission as an indicator of the aggravated in-hospital outcome as well as of increased health care resources demand [2].

### 2.2. ETHICAL ASPECTS and STUDY OVERSIGHT

Since our study did not include direct access of us to individual patient data but instead only access to summarised and aggregated results, which are/were provided by the RDC, an approval by the ethics committee, as well as patients' informed consent, were not required, in accordance with German law [2].

### 2.3. Coding of diagnoses, surgeries, procedures and definitions

Germany is the most populous country in the European Union, with more than 80 million citizens. In 2004, diagnosis- and procedure-related coding for remuneration was introduced. This coding must be done according to the German Diagnosis Related Groups (G-DRG) system comprising patient data on diagnoses, coexisting conditions, surgeries,

and procedures/interventions. For the hospitals it is mandatory to transfer these codes to the Institute for the Hospital Remuneration System to receive their remuneration [2]. Patients' diagnoses have to be coded according to the International Statistical Classification of Diseases and Related Health Problems, 10th revision, with German modification (ICD-10-GM) [2]. Additionally, surgical, diagnostical and interventional procedures are coded with OPS codes (Operationen-und Prozedurenschlüssel) to capture the costs of patients' hospitalizations. In the present analysis of the German NIS, we identified all hospitalized children with a confirmed COVID-19 diagnosis (ICD-code U07.1) in Germany during the year 2020 (COVID-19 as main or secondary diagnosis).

Post-COVID status was defined as status of previous survived COVID-19-infection (before the patient's hospitalization with the actual COVID-19 infection). Obesity was defined as body mass index  $\geq 30$  kg/m<sup>2</sup> according to the recommendations of the WHO (World Health Organization) [13,14].

### 2.4. Statistical analysis

All hospitalized COVID-19 patients aged  $\leq 18$  years in Germany were stratified for admission to an ICU.

Differences in patient characteristics between hospitalized COVID-19 patients with and without ICU admission were compared by Wilcoxon-Mann-Whitney-U-test for continuous variables and Fisher's exact or chi<sup>2</sup> test for categorical variables, as appropriate. Temporal trends regarding the necessity of ICU in COVID-19 patients over time and with age were estimated using linear regression analyses. The computed results are presented as beta ( $\beta$ )-estimates with corresponding 95 % confidence intervals (CI).

We calculated logistic regression models to investigate associations between patients' characteristics, cardiovascular risk factors, and comorbidities as well as manifestations of COVID-19 adverse events and the necessity of mechanical ventilation on the one hand and admission to ICU on the other hand. Results were presented as odds ratios (OR) and 95 % confidence intervals (CI). The multivariable regression models were sequentially adjusted for I) sex and additionally for II) age, sex, diabetes mellitus, cancer, heart failure, chronic obstructive pulmonary disease (COPD), chronic renal insufficiency (glomerular filtration rate  $< 60$  ml/min/1.73 m<sup>2</sup>), and obesity. We selected this statistical approach regarding the adjustment to minimize confounding by the adjustment-included parameters, which are well-known to be associated with aggravated outcomes during hospitalization.

All statistical analyses were computed with the SPSS software (IBM Corp. Released 2011. IBM SPSS Statistics for Windows, Version 20.0. IBM Corp: Armonk, NY, USA). In the present analysis, P values should be treated as a continuous measure of the statistical strength of an association, and they are therefore reported exactly. However, for descriptive reasons, p values of  $< 0.05$  (two-sided) were referred to as statistically significant. No adjustment for multiple testing was applied due to the explorative nature of the analysis.

## 3. Results

Overall, 3360 hospitalizations of children (median age 7.0 [IQR 0.0–15.0] years, 49.8 % of female sex) with confirmed COVID-19 infection were counted in Germany during the year 2020. Among these, 144 (4.3 %) had to be admitted to an ICU, and eight (0.2 %) died during the in-hospital course (Table 1). While the ICU admission rate of children with COVID-19 aged  $\leq 6$  years was 3.7 %, the admission rate increased in children aged 7 to  $\leq 12$  years to 6.2 % and was 4.4 % in children with COVID-19 aged 13 to  $\leq 18$  years.

While the monthly absolute numbers of hospitalizations of infected children aged  $\leq 18$  years were highest in the last quarter of the year 2020, the highest rate of ICU admissions was observed in spring and summer (Fig. 1A). In this context, the highest demand for ICU admission was demonstrated for the first decade of life (Fig. 1B).

**Table 1**

Patients' characteristics, medical history, presentation and adverse in-hospital events of the 3360 hospitalized children with confirmed COVID-19 infection in Germany in the year 2020 stratified for ICU treatment.

Parameters	All hospitalized children with COVID-19 aged ≤18 years (n = 3360; 100.0 %)	Children with COVID-19, who were treated on normal ward (n = 3216; 95.7 %)	Children with COVID-19, who were treated on ICU (n = 144; 4.3 %)	P-value
Age (years)		7.0 (0.0–15.0)	8.0 (2.0–16.0)	<b>0.007</b>
Female sex	1674 (49.8 %)	1611 (50.1 %)	63 (43.8 %)	0.136
Length of in-hospital stay		2.0 (1.0–4.0)	10.0 (5.0–16.8)	<b>&lt;0.001</b>
Cardiovascular risk factors				
Obesity	42 (1.3 %)	37 (1.2 %)	5 (3.5 %)	<b>0.032</b>
Essential arterial hypertension	18 (0.5 %)	14 (0.4 %)	4 (2.8 %)	<b>&lt;0.001</b>
Diabetes mellitus	47 (1.4 %)	36 (1.1 %)	11 (7.6 %)	<b>&lt;0.001</b>
- Diabetes mellitus type I	39 (1.2 %)	29 (0.9 %)	10 (6.9 %)	<b>&lt;0.001</b>
- Diabetes mellitus type II	3 (0.1 %)	3 (0.1 %)	0 (0 %)	1.000
Comorbidities				
Coronary artery disease	3 (0.1 %)	3 (0.1 %)	0 (0 %)	1.000
Heart failure	25 (0.7 %)	6 (0.2 %)	19 (13.2 %)	<b>&lt;0.001</b>
Atrial fibrillation/flutter	3 (0.1 %)	3 (0.1 %)	0 (0.0 %)	1.000
Acute and chronic lung diseases (including Asthma bronchiale, chronic obstructive pulmonary disease, emphysema, and/or bronchiectasis)	67 (2.0 %)	63 (2.0 %)	4 (2.8 %)	0.532
Asthma bronchiale	59 (1.8 %)	56 (1.7 %)	3 (2.1 %)	0.740
Acute and/or chronic kidney failure	41 (1.2 %)	27 (0.8 %)	14 (9.7 %)	<b>&lt;0.001</b>
Cancer	64 (1.9 %)	52 (1.6 %)	12 (8.3 %)	<b>&lt;0.001</b>
Hepatitis	3 (0.1 %)	3 (0.1 %)	0 (0.0 %)	1.000
Liver disease	31 (0.9 %)	24 (0.7 %)	7 (4.9 %)	<b>&lt;0.001</b>
Severe liver disease	22 (0.7 %)	17 (0.5 %)	5 (3.5 %)	<b>0.002</b>
Manifestations of COVID-19				
Acute bronchitis	82 (2.4 %)	77 (2.4 %)	5 (3.5 %)	0.399
Pneumonia	214 (6.4 %)	168 (5.2 %)	46 (31.9 %)	<b>&lt;0.001</b>
Acute respiratory distress syndrome	13 (0.4 %)	3 (0.1 %)	10 (6.9 %)	<b>&lt;0.001</b>
Vasculopathy	23 (0.7 %)	19 (0.6 %)	4 (2.8 %)	<b>0.015</b>
Multisystem Inflammatory syndrome caused by COVID-19	22 (0.7 %)	10 (0.3 %)	12 (8.3 %)	<b>&lt;0.001</b>
Post-COVID-19 status	7 (0.2 %)	7 (0.2 %)	0 (0.0 %)	1.000
Treatment				
Extracorporeal membrane oxygenation (ECMO)	4 (0.1 %)	0 (0.0 %)	4 (2.8 %)	<b>&lt;0.001</b>
Dialysis	7 (0.2 %)	a	a	<b>0.033</b>
Adverse events during hospitalization				
In-hospital case-fatality	8 (0.2 %)	3 (0.1 %)	5 (3.5 %)	<b>&lt;0.001</b>
Venous thromboembolism	6 (0.2 %)	a	a	<b>&lt;0.001</b>
Acute kidney failure	21 (0.6 %)	11 (0.3 %)	10 (6.9 %)	<b>&lt;0.001</b>
Myocarditis	20 (0.6 %)	10 (0.3 %)	10 (6.9 %)	<b>&lt;0.001</b>
Myocardial infarction	0 (0 %)	0 (0 %)	0 (0 %)	1.000
Stroke (ischaemic or haemorrhagic)	3 (0.1 %)	0 (0 %)	3 (2.1 %)	<b>&lt;0.001</b>
Intracerebral bleeding	0 (0 %)	0 (0 %)	0 (0 %)	1.000
Transfusion of blood constituents	76 (2.3 %)	45 (1.4 %)	31 (21.5 %)	<b>&lt;0.001</b>

<sup>a</sup> due to confidentiality reasons, the data cannot be shown.

We detected regional differences regarding ICU admissions: Highest rates of ICU admissions were seen in the federal states of Berlin, Hamburg, and Baden-Württemberg (Fig. 2A). Most children were treated in hospitals located in urban areas with the highest demand for ICU admissions (Fig. 2B).

### 3.1. Comparison of children aged ≤18 years with confirmed COVID-19 infection admitted to ICU vs. those without ICU admission

Children with confirmed COVID-19 infection admitted to ICU were slightly older (8.0 [2.0–16.0] vs. 7.0 [0.0–15.0] years,  $P = 0.007$ ) and more often of male sex (56.2 % vs. 49.9 %,  $P = 0.136$ ) in comparison to those treated on normal floors (Table 1). As expected, the length of in-hospital stay was negatively affected by ICU admission (10.0 [5.0–16.8] vs. 2.0 [1.0–4.0],  $P < 0.001$ ).

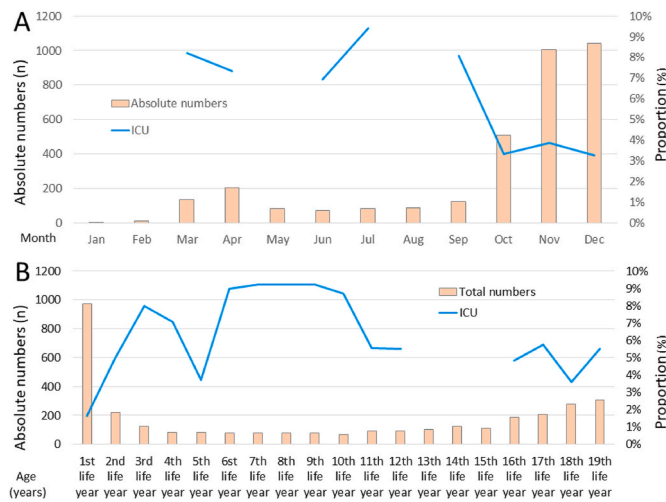
Since COVID-19 infection is primarily an infectious disease of the lungs, pneumonia (31.9 % vs. 5.2 %,  $P < 0.001$ ) and acute respiratory distress syndrome (ARDS) (6.9 % vs. 0.1 %,  $P < 0.001$ ) were both substantially more often detected in children with confirmed COVID-19 infection admitted to ICU than in those without ICU-admission. In addition, multisystem inflammatory syndrome caused by COVID-19 (8.3 % vs. 0.3 %,  $P < 0.001$ ) and vasculopathy (2.8 % vs. 0.6 %,  $P = 0.015$ ) were more commonly treated on the ICU (Table 1).

However, also other patient characteristics and comorbidities were identified to be more frequent in those children admitted to ICU: Children with COVID-19 who were treated on ICU revealed more often cardiovascular risk factors like obesity (3.5 % vs. 1.2 %,  $P = 0.032$ ) and especially diabetes mellitus (7.6 % vs. 1.1 %,  $P < 0.001$ ) and comorbidities such as heart failure (13.2 % vs. 0.2 %,  $P < 0.001$ ), acute and/or chronic kidney failure (9.7 % vs. 0.8 %,  $P < 0.001$ ), cancer (8.3 % vs. 1.6 %,  $P < 0.001$ ) and liver disease (4.9 % vs. 0.7 %,  $P < 0.001$ ) (Table 1).

### 3.2. Independent factors associated with ICU admission

In childhood patients with COVID-19, the lung manifestations pneumonia (OR 7.373 [95%CI 4.823–11.271],  $P < 0.001$ ) and ARDS (OR 48.058 [95%CI 11.689–197.588],  $P < 0.001$ ) were independently associated with an aggravated disease course and ICU admission, whereas multisystem inflammatory syndrome caused by COVID-19 was also a strong predictor for ICU admission (OR 9.573 [95%CI 3.036–30.191],  $P < 0.001$ ) (Table 2).

The established cardiovascular risk factors obesity (OR 3.419 [95%CI 1.300–8.993],  $P = 0.013$ ) and diabetes mellitus (OR 6.929 [95%CI 3.327–14.432],  $P < 0.001$ ) were also independent risk factors for ICU admission. Regarding cardiovascular diseases, heart failure (OR 64.509



**Fig. 1.** Temporal trends regarding total numbers of hospitalized childhood patients with COVID-19-infection and necessity of intensive care unit treatment (ICU)

**Panel A** – Monthly trends regarding absolute numbers of hospitalized childhood patients  $\leq 18$  years with COVID-19-infection and proportion regarding necessity of intensive care unit treatment (ICU).

**Panel B** – Temporal trends regarding absolute numbers of hospitalized childhood patients with COVID-19-infection stratified by age and proportion regarding necessity of intensive care unit treatment (ICU).

[95%CI 24.462–170.121],  $P < 0.001$ ) and myocarditis (OR 4.682 [95% CI 1.278–17.149],  $P = 0.020$ ) were strongly associated with the need of ICU admission (Table 2). Among the other investigated comorbidities, acute and/or chronic kidney failure (OR 7.946 [95%CI 3.606–17.508],  $P < 0.001$ ), cancer (OR 5.220 [95%CI 2.599–10.485],  $P < 0.001$ ), liver diseases (OR 5.501 [95%CI 2.177–13.899],  $P < 0.001$ ), and venous

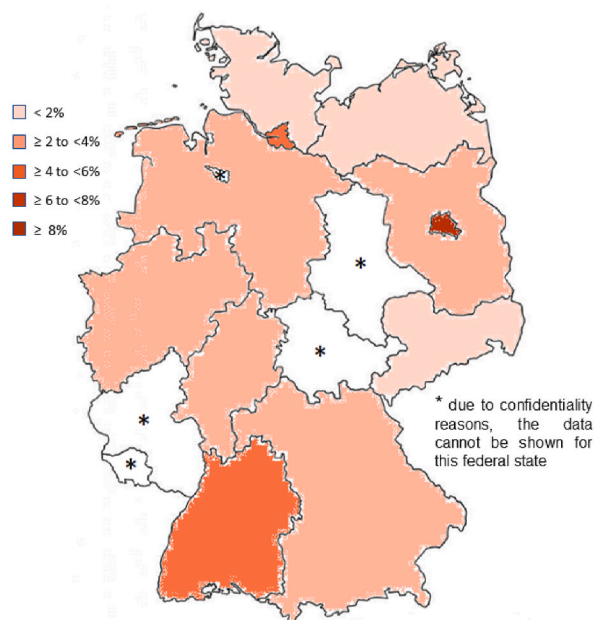
thromboembolism (VTE) (95%CI 38.638 [95%CI 6.253–238.729],  $P < 0.001$ ) were also associated with ICU admission (Table 2).

**3.3. Prevalence of adverse events during hospitalizations of children aged  $\leq 18$  years with confirmed COVID-19 infection admitted to ICU in comparison to those without ICU admission**

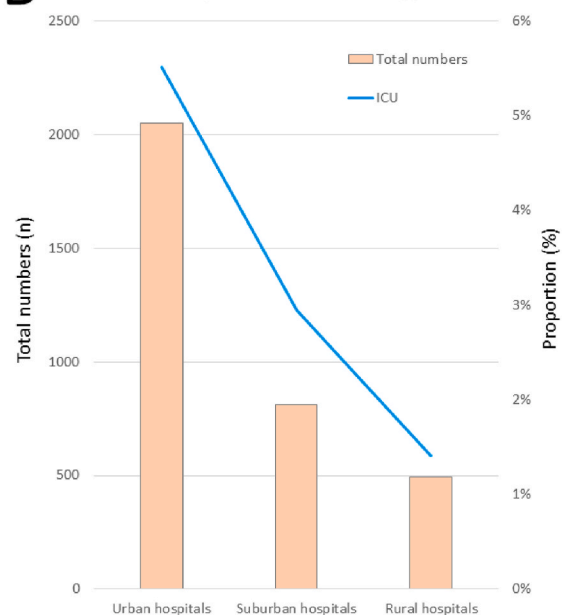
In-hospital death occurred in five patients with and three without ICU admission (3.5 % vs. 0.1 %,  $P < 0.001$ ) (Table 1). Myocarditis (6.9 % vs. 0.3 %,  $P < 0.001$ ) and stroke (ischaemic or haemorrhagic, 2.1 % vs. 0 %,  $P < 0.001$ ) were both more often observed in children admitted to ICU. Of the 10 children with myocarditis events, half of these children with myocarditis, who were treated on ICU, revealed a myocarditis in co-prevalence with a multisystem inflammatory syndrome. Regarding bleeding events, transfusion of blood constituents was also more often needed in patients with ICU admission (21.5 % vs. 1.4 %,  $P < 0.001$ ) (Table 1). Overall, 27.8 % of the children admitted to ICU had to be treated with mechanical ventilation. As expected, ICU admission was independently associated with increased case-fatality (univariate regression: OR 38.525 [95 % CI 9.115–162.830],  $P < 0.001$ ; multivariate regression adjusted for sex: OR 21.573 [95%CI 4.191–111.044],  $P < 0.001$ ; multivariate regression adjusted for sex, diabetes mellitus, cancer, heart failure, chronic obstructive pulmonary disease (COPD), chronic renal insufficiency (glomerular filtration rate  $< 60$  ml/min/1,73 m<sup>2</sup>) and obesity: OR 21.573 [95%CI 4.191–111.044],  $P < 0.001$ ).

This association between necessity of ICU admission and in-hospital death was stronger in later childhood illustrated in children aged 13 to  $\leq 18$  years (univariate logistic regression: OR 45.569 [95%CI 4.065–510.810],  $P = 0.002$ ) than in children aged 7 to  $\leq 12$  years (univariate logistic regression: OR 32.552 [95%CI 2.867–369.591],  $P = 0.005$ ) and children aged  $\leq 6$  years (univariate logistic regression: OR 26.763 [95%CI 1.654–433.102],  $P = 0.021$ ).

**A Admission rate to intensive care units**



**B Hospital and area type**



**Fig. 2.** Regional differences regarding total numbers regarding admission rate on intensive care units (ICU) of hospitalized childhood patients with COVID-19-infection

**Panel A** – Admission rate on intensive care units (ICU) of hospitalized childhood patients with COVID-19-infection in the different federal states of Germany

**Panel B** – Regional trends of hospitalized childhood patients with COVID-19-infection and regarding admission rate on intensive care units (ICU) in hospitals of different area types.

**Table 2**

Impact of patient-characteristics and conditions on admission at the ICU of the 3360 hospitalized children with confirmed COVID-19 infection in Germany in the year 2020 (univariate and multivariate logistic regression model).

	Univariate regression		Multivariate regression <sup>a</sup>		Multivariate regression <sup>b</sup>	
	OR (95 % CI)	P-value	OR (95 % CI)	P-value	OR (95 % CI)	P-value
Female sex	0.775 (0.554–1.085)	0.137	0.775 (0.554–1.085)	0.137	0.730 (0.509–1.047)	0.087
<b>Cardiovascular risk factors and comorbidities</b>						
Obesity	3.091 (1.196–7.985)	<b>0.020</b>	3.156 (1.220–8.164)	<b>0.018</b>	3.419 (1.300–8.993)	<b>0.013</b>
Arterial hypertension	6.535 (2.124–20.108)	<b>0.001</b>	6.557 (2.127–20.209)	<b>0.001</b>	3.416 (0.953–12.241)	0.059
Diabetes mellitus	7.306 (3.638–14.670)	<b>&lt;0.001</b>	7.312 (3.638–14.697)	<b>&lt;0.001</b>	6.929 (3.327–14.432)	<b>&lt;0.001</b>
Heart failure	81.320 (31.923–207.154)	<b>&lt;0.001</b>	81.034 (31.768–206.698)	<b>&lt;0.001</b>	64.509 (24.462–170.121)	<b>&lt;0.001</b>
Myocarditis	23.925 (9.792–58.460)	<b>&lt;0.001</b>	23.523 (9.612–57.566)	<b>&lt;0.001</b>	4.682 (1.278–17.149)	<b>0.020</b>
Acute and/or chronic kidney failure	12.720 (6.516–24.830)	<b>&lt;0.001</b>	12.932 (6.612–25.292)	<b>&lt;0.001</b>	7.946 (3.606–17.508)	<b>&lt;0.001</b>
Acute kidney failure	21.744 (9.076–52.089)	<b>&lt;0.001</b>	22.070 (9.191–52.996)	<b>&lt;0.001</b>	9.835 (3.261–29.665)	<b>&lt;0.001</b>
Acute and chronic lung diseases (including Asthma bronchiale bronchitis, chronic obstructive pulmonary disease, emphysema, and/or bronchiectasis)	1.430 (0.513–3.984)	0.494	1.451 (0.520–4.045)	0.477	1.453 (0.510–4.136)	0.484
Asthma bronchiale	1.201 (0.371–3.883)	0.760	1.220 (0.377–3.948)	0.740	0.580 (0.047–7.149)	0.671
Cancer	5.531 (2.884–10.611)	<b>&lt;0.001</b>	5.442 (2.835–10.449)	<b>&lt;0.001</b>	5.220 (2.599–10.485)	<b>&lt;0.001</b>
Liver disease	6.796 (2.878–16.045)	<b>&lt;0.001</b>	6.684 (2.827–15.801)	<b>&lt;0.001</b>	5.501 (2.177–13.899)	<b>&lt;0.001</b>
Venous thromboembolism	45.914 (8.339–252.792)	<b>0.002</b>	44.509 (8.062–245.737)	<b>&lt;0.001</b>	38.638 (6.253–238.729)	<b>&lt;0.001</b>
Gastro-intestinal bleeding	2.502 (0.575–10.889)	0.222	2.444 (0.561–10.647)	0.234	1.538 (0.217–10.888)	0.666
<b>Manifestations of COVID-19</b>						
Acute bronchitis	1.466 (0.584–3.681)	0.415	1.454 (0.579–3.651)	0.426	1.662 (0.655–4.216)	0.285
Pneumonia	8.516 (5.805–12.493)	<b>&lt;0.001</b>	8.472 (5.773–12.433)	<b>&lt;0.001</b>	7.373 (4.823–11.271)	<b>&lt;0.001</b>
Acute respiratory distress syndrome	79.925 (21.745–293.777)	<b>&lt;0.001</b>	82.000 (22.240–302.346)	<b>&lt;0.001</b>	48.058 (11.689–197.588)	<b>&lt;0.001</b>
Vasculopathy	4.808 (1.614–14.319)	<b>0.005</b>	4.793 (1.607–14.294)	<b>0.005</b>	1.356 (0.308–5.961)	0.687
Multisystem inflammatory syndrome caused by COVID-19	29.145 (12.369–68.674)	<b>&lt;0.001</b>	29.055 (12.311–68.572)	<b>&lt;0.001</b>	9.573 (3.036–30.191)	<b>&lt;0.001</b>

<sup>a</sup> Adjusted for sex.

<sup>b</sup> Adjusted for age, sex, heart failure, acute and chronic lung diseases (including Asthma bronchiale bronchitis, chronic obstructive pulmonary disease, emphysema, and/or bronchiectasis), and acute and/or chronic kidney failure.

#### 4. Discussion

Since most children experience a mild course of COVID-19 after SARS-CoV-2-infection in comparison to adults and an asymptomatic infection is common [9,15,16], children represent an underestimated and insufficiently studied patient group in the COVID-19 pandemic [2,6,7,9–12]. Nevertheless, early identification of children who must be monitored for life-threatening severe COVID-19 course remains difficult [9]. We aimed to close this gap with the identification of associated factors with aggravated COVID-19 disease course continuously with paediatric intensive care unit (ICU) admissions in Germany, since the understanding of risk factors for ICU admission as one important bottleneck of adequate management regarding escalated treatment of COVID-19 pandemic is of outstanding interest to understand determinants, which are both crucial factors for adequate health care planning, decision making and pandemic management [2,3,9,17].

Compared to other already published studies, the proportion of paediatric patients with confirmed COVID-19 infection admitted to ICU in Germany was low [16]. While the proportion of hospitalized children admitted to ICU was 4.3 % in German hospitals during the year 2020, which was similar to the rate of 4.0 % reported by Garazzino et al. for an Italian multi-centre study [18], most other studies and registries reported higher proportions of treated children in different countries [11,16,19]: in a retrospective study analysing more than 12,000 paediatric COVID-19 patients in the United States, the ICU admission rate

regarding hospitalized patients was distinctly higher with 17.6 % [16]. Also, Göttinger et al. reported in their European multi-center study a higher ICU admission rate of 8.0 % [11] in comparison to our findings and one Iranian study described an ICU admission rate of paediatric COVID-19 patients of even 42.4 % [19]. These differences regarding ICU admission rates are most probably driven by inter-country health care variations and maybe also influenced by ICU capacities in these different countries. While most hospitalizations of children and young people with COVID-19 in Germany were detected in fall and winter of 2020, the highest proportion of ICU admissions was needed in the summer of 2020. It has to be mentioned that the results of our study were not influenced by SARS-CoV-2 vaccination since the vaccination program against SARS-CoV-2 for adults started in Germany (similarly to most European countries), not before December 2020 and approval for vaccines regarding children aged 12 years and older was not implemented before mid of the year 2021 [3].

The course of COVID-19 infection in children is commonly of short duration and accompanied by low symptom burden. Nevertheless, some infected children revealed a prolonged and aggravated illness [9,15,16]. In accordance with other studies, our study confirmed a lower in-hospital rate of adverse events in children compared to adult hospitalized COVID-19 patients [2,9,16]. While a high in-hospital case-fatality rate of 17.9 % during the year 2020 was reported for all hospitalizations of patients with confirmed COVID-19-infection [2], our present study showed, fortunately, a very low in-hospital case-fatality

rate of 0.1 % in children treated on normal ward and 3.5 % in hospitalized children with COVID-19, who had to be admitted on ICU. Thus, the aggravated course of COVID-19 accompanied by necessity of ICU admission was related to a substantially increased mortality, as expected [2,3,11].

The case-fatality rate of 3.5 % of pediatric patients with confirmed COVID-19 infection in Germany was in line with other previously published studies, showing an overall case-fatality rate in children of 0.1%–0.7 % in European countries, China, and the United States in general [9, 11,12,20], and of 1.4%–40.0 % in pediatric patients treated on ICU [21–24]. Garazzino et al. [18] demonstrated a complication rate according to occurrence of adverse events of 38.8 % of hospitalized pediatric COVID-19 patients [18].

It is well established that a high burden of comorbid conditions was associated with poor clinical outcomes in adult patients with COVID-19 [2,16]. Children usually do not have multiple comorbid conditions, but a small number of pre-existing comorbidities in children might already be accompanied by the aggravated course of COVID-19 in children [9, 12,16,18,19,24]. In this context, comorbidities have been reported as an essential key factor for a more severe course of COVID-19 being present in 50–82 % of children admitted to ICU [19,24]. In accordance with the literature, in our study, children, who were admitted to ICU, and therefore, comprising those with aggravated hospitalization course were more often of male sex, had more often pneumonia or ARDS, multisystem inflammatory syndrome, vasculopathy, and more often comorbidities such as obesity, diabetes mellitus, heart failure, myocarditis, acute and/or chronic kidney failure, cancer and liver disease. Thus, these findings are in line with previously published data, revealing that younger age, male sex and higher comorbidity burden are accompanied with elevated risk for severe COVID-19 [9].

In accordance with previously published studies, our results revealed that younger age, male sex, obesity, and diabetes mellitus were risk factors for a severe COVID-19 course in children [4,9,10,22]. In our study, children with confirmed COVID-19 infection aged 7 to  $\leq 12$  years had the highest admission rate on paediatric ICU. In another study, age between 5 and 9 years was related to highest rates of ICU admission, which might be caused by viral co-infections [18].

Children admitted to paediatric ICU were more often of male sex than those treated on a normal ward, which is in line with some [24], but not with all studies [18]. Obesity was in our study and previously published studies among hospitalized COVID-positive children associated with a more severe course of COVID-19 [2,10]. In our study, obesity was affected by a 3.4-fold increased risk of admission to an ICU. In this context, it is important that the prevalence of overweight and obesity in children is steadily rising in the European region [25]. The World Obesity Federation estimated that obesity will afflict 206 million children and adolescents aged 5–19 years in 2025 and 254 million in 2030 [25].

Besides obesity, diabetes mellitus as a obesity-related disease was also associated with approximately 7-times raised risk for ICU admission. This finding is in accordance with other studies detecting a higher rate of diabetes mellitus in pediatric ICU patients during COVID-19 pandemic [22,26].

As COVID-19 is primarily a respiratory illness, it is not surprising that severe lung manifestations like pneumonia and ARDS are both strong predictors of ICU admission [24]. Asthma bronchial was initially thought to bear an increased risk for more severe COVID-19. However, our study showed no association of asthma bronchial as a comorbidity with ICU admission in contrast to others [10]. Beside the lung as the primary localization, COVID-19 might also cause injuries of heart, kidney, and liver [7]. Cardiac complications, in particular myocarditis, pericarditis and resulting heart failure, could be the result of SARS-CoV-2 infection [2,8,9]. In the present study, myocarditis and heart failure were both strongly and independently associated with ICU admission.

As aforementioned, although the SARS-CoV2 targets primarily the

lungs, it is not uncommon that it also affects other organ systems like the kidneys [21]. Kidney injury was identified as independent risk factor for ICU admission in our study. Acute kidney injury was coded in 6.9 % of the children admitted on ICU and therefore, it occurred 23-times more often in those paediatric patients admitted on ICU in comparison to those treated on normal ward. Other studies identified an even higher proportion of acute kidney injury (18–44 %) in paediatric patients admitted to ICU [21,23].

Liver injury is another mentioned organ manifestation of SARS-CoV-2 [27,28]. Data of different studies indicate that between 2 and 11 % of patients with COVID-19 had liver comorbid conditions, and between 14 and 53 % of the patients develop liver markers during COVID-19 infection [27]. Notable, patients with severe COVID-19 are afflicted by higher rates of liver dysfunction (up to 62 %) [1,27]. Liver injury/disease was coded in 4.9 % of the children admitted to ICU and liver disease was independently related to the necessity of ICU treatment. Liver damage in mild cases of COVID-19 is often transient with restitution without any specific treatment. The etiology of COVID-19-related liver damage comprises the following causes [28]: I) Liver damage in COVID-19 patients might be directly caused by viral infection of liver cells [1,28]. II) Another direct mechanism comprises binding of SARS-CoV-2 to angiotensin-converting enzyme 2 in the liver or bile duct resulting in direct toxicity. III) Indirect mechanisms include an inflammatory immune response and the effect of hypoxia as well as hepatotoxicity of COVID-19-related treatments [28,29].

Although children infected by COVID-19 with cancer might have better outcomes than adults with cancer in general, cancer is afflicted with an elevated risk of hospitalization, ICU admission, and also death compared to the general paediatric population [30]. In accordance, cancer comorbidity in children was in our present study independently associated with 5-fold risk of ICU admission.

In addition, multisystem inflammatory syndrome caused by COVID-19 was strongly and independently associated with ICU admission. Multisystem inflammatory syndrome caused by COVID-19 was detected in 8.3 % of the admitted children on ICU and, therefore was approximately 28-fold more common in ICU patients in comparison to those treated in the normal ward. The reported prevalence of multisystem inflammatory syndrome caused by COVID-19 varies widely in the literature between 23.9 and 74.3 % [21].

Soon after the COVID-19 pandemic outbreak, reports about paediatric patient cases with unusual febrile illnesses and vasculopathy, such as Kawasaki's disease, were published [31,32]. Nevertheless, data regarding the incidence/prevalence of these rare vascular complications in children with COVID-19 are sparse. We detected a vasculopathy frequency of 2.8 % in paediatric COVID-19 patients admitted to ICU. Since these vasculopathies in relation to COVID-19 infection often occur in co-prevalence with other immunological conditions [31,32], vasculopathy was not an independent risk factor for ICU admission. It is well known that children with vasculopathy and multisystem inflammatory syndrome are more prone to develop severe cardiac symptoms and these cardiac complications are the main reasons for requiring ICU treatments [10].

The SARS-CoV-2 pandemic was accompanied by a grave strain on healthcare systems worldwide, underlining that adequate paediatric services resources must be allocated and provided to sustain the strain on healthcare systems guarantee high-quality medicine, and reach the best outcomes for children and young people [11].

Our findings have several public health care implications: For appropriately management of severe COVID-19 cases, treating physicians should raise their awareness regarding risk factors for the aggravated course of COVID-19 in paediatric patients [9].

Early identification of children afflicted with increased risk for severe COVID-19 course is essential for health care service planning since ICU resources are the bottleneck of health care service and outstanding importance for adequate complication management in this crucial patient group [3,9]. In this context, admission of children with threatening

severe COVID-19 in adequately equipped and structured ICU seems to be essential to improve disease outcomes [9].

## 5. Limitations

The following limitations of the present study must be mentioned: Data structure of reimbursement data with ICD- and OPS-code-based study-analysis of hospitalized patients of the German nationwide-inpatient sample, under-reporting as well as under-coding are possible, and data on most concomitant medication or laboratory markers are not available. Additionally, follow-up evaluation after discharge from the hospital is not possible and available since data are limited to the time frame of the in-hospital course. Small event number, unbalanced groups, and huge confidence intervals makes it difficult to estimate the localization of the „true effect“.

## 6. Conclusions

The proportion of hospitalized pediatric COVID-19 patients admitted to ICU in Germany was low with 4.3 %. While ICU admission was independently associated with increased case-fatality, the case-fatality rate of children with a necessity of ICU was also low with 3.5 % in comparison to other countries. Independent factors associated with ICU admission were obesity, diabetes mellitus, pneumonia, ARDS, multi-system inflammatory syndrome caused by COVID-19, heart failure, myocarditis, acute and/or chronic kidney failure, cancer, liver diseases, and VTE.

## CRedit authorship contribution statement

**Karsten Keller:** Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Software, Resources, Project administration, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Ingo Sagoschen:** Writing – review & editing. **Volker H. Schmitt:** Writing – review & editing. **Visvakanth Sivanathan:** Writing – review & editing. **Ioannis T. Farmakis:** Writing – review & editing. **Omar Hahad:** Writing – review & editing. **Sebastian Koelmel:** Writing – review & editing. **Frank P. Schmidt:** Writing – review & editing. **Christine Espinola-Klein:** Writing – review & editing. **Stavros Konstantinides:** Writing – review & editing. **Thomas Münzel:** Writing – review & editing. **Philipp Lurz:** Writing – review & editing. **Lukas Hobohm:** Writing – review & editing, Project administration, Methodology, Investigation, Conceptualization.

## Ethical statement

Since our study did not comprise direct access by the investigators to individual patient data but only an access to summarised results provided by the RDC, approval by an ethics committee as well as patients' informed consent were not required, in accordance with German law.

## Data sharing

The statistics of this study was carried out on our behalf by the Research Data Center (RDC) of the Federal Bureau of Statistics (Wiesbaden, Germany) analysing the nationwide inpatient sample (NIS) of Germany (source: RDC of the Federal Statistical Office and the Statistical Offices of the federal states, DRG Statistics 2020, own calculations).

All codes used in this study are publicly available online. The data used in this study are aggregated study analysis results provided by the RDC; thus, we had access to summarised results provided by the RDC, but no access to individual patient-level data, which will not be made publicly available.

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## Declaration of Competing interest

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