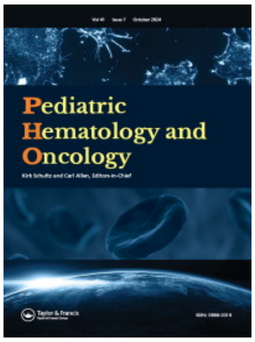

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Impact of regional SARS-CoV-2 proceedings on changes in diagnoses of pediatric malignancies in Bavaria during the COVID-19 pandemic

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ABSTRACT
The COVID-19 pandemic affected daily life significantly and had massive consequences for healthcare systems with tremendous regional differences. This retrospective study aimed to investigate whether the pandemic and resulting societal changes impacted the diagnosis of pediatric malignancies in a distinct region. Pediatric cancer cases in Bavaria (2016–2021) and SARS-CoV-2 proceedings during the peak phase of the pandemic (2020–2021) were retrospectively analyzed. All new diagnoses of pediatric malignancies reported from cancer centers in Bavaria were included. Clinical data from pre-pandemic years was compared to diagnoses made during the pandemic. Official SARS-CoV-2 reports were received from the Bavarian Health and Food Safety Authority and data on regional pandemic measures were obtained from the Healthcare Data Platform. With this design, a comprehensive analysis of the pandemic proceedings was performed. We found significantly decreased incidence-rate ratios for pediatric cancer diagnosis during the early spring peak of SARS-CoV-2 as it was observed in May during the pandemic, followed by non-significantly increased metastatic cancer diagnosis two months later. Additionally, the time-to-diagnosis of pediatric malignancies was significantly prolonged during the pandemic, and outpatient contacts were significantly reduced, although the availability of consultations remained

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the same. From our findings, we may hypothesize that there have been effects on pediatric cancer diagnosis during the COVID-19 pandemic at vulnerable times. Interpretation of changes remains speculative with potential causes from behavior patterns, such as hesitation, concerns, and potential societal changes during phases of public restrictions, rather than overwhelmed medical capacities. Nevertheless, specific awareness is needed to protect this patient population during potential future pandemics.

Introduction

The outbreak of the novel severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), which causes coronavirus-disease-2019 (COVID-19), quickly initiated a global pandemic that significantly impacted daily life since its beginning in 2020. Due to the rapid development of the pandemic, the behavior of populations and medical institutions changed across the globe. Medical care and management of cancer patients were challenged.[1–3] Shortly after the outbreak of the pandemic, measures like social distancing, contact restrictions, curfew, and shutdowns were implemented in most countries to contain the spread of SARS-CoV-2 and avoid a collapse of the healthcare system. Pandemic restrictions, however, not only influenced the spread of SARS-CoV-2 but also the behavior and quality of life of societies, especially families and children,[4,5] as well as the willingness of parents to access pediatric healthcare.[6]

Various reports from around the world demonstrated significant changes in cancer diagnoses, i.e. fewer cases of newly identified cancer and shift to later stages during the start of the COVID-19 pandemic.[7–9] Most of the reports focused on adults, but also for children and young adults, significant changes were identified. Decreased diagnoses of pediatric malignancies were indicated during the first wave of the pandemic, with several studies identifying delays in presentation and access or provision of care.[10–15] In addition, changes in pediatric oncology service provision were identified in a large international cohort study that explored the effect of the COVID-19 pandemic on pediatric oncology care.[16] However, mainly data from single institutions or the beginning of the pandemic were reported. For Germany, data from the German Childhood Cancer Registry (GCCR), a population-based childhood cancer registry, that monitors incident cases of all malignancies diagnosed in pediatric patients across the nation, were published for 2020 showing a slight increase in childhood cancer diagnoses with no effect on distribution among age and entities.[17] GCCR speculated that the unexpected increase might have resulted from greater parental attention to early disease symptoms in their child during the pandemic and thus timelier consultations and diagnoses. GCCR updated their analyses with data from 2021 and observed a rebound effect from increased diagnoses in 2021 for some diagnostic groups, but not for others.[18] The underlying reasons for the noted changes remain unclear and GCCR states that they are e.g. lacking information regarding the stage at diagnosis, to further examine the potential reasons for the observations. Pandemic proceedings and restrictions should also be taken into consideration with further investigations. Since the regional incidence of SARS-CoV-2 was variable and public restrictions were not uniform, however, conclusions from the currently published literature are difficult. Further analyses of consistent regional data sets during the course of the pandemic are needed, including disease stage at diagnosis to improve understanding of possible influences of the pandemic on pediatric malignancies.

Looking back on the pandemic, questions if and how much the pandemic and corresponding restrictions impacted the healthcare system and, whether the wellbeing of children was jeopardized, remain. Concern for (indirect) impact on childhood cancer diagnoses cannot be neglected, thus, we conducted a retrospective analysis of pediatric malignancy diagnoses during the most affected years of the COVID-19 pandemic. Data were captured in Bavaria, a federal state in the south of Germany with six academic pediatric cancer centers that are part of the Pediatric Oncology Network Bavaria (KIONET). Whereas different federal states in Germany were subject to different pandemic restrictions during 2020–2021, regulations in Bavaria were largely uniform. Using both clinical data, as well as data on SARS-CoV-2 incidence and pandemic restrictions, the aim of this study was to examine the impact of the COVID-19 pandemic on the incidence of newly diagnosed pediatric malignancies, stage, and time-to-diagnosis (TTD).

Material and methods

Clinical data

All six academic pediatric cancer centers in Bavaria, Augsburg, Erlangen, LMU Munich, TU Munich, Regensburg, and Würzburg (alphabetical order) reported newly diagnosed hematologic and solid malignancies in children (0 < 18 years) from 01-January-2016 to 31-December-2021 according to their local documentation, following guidelines for reporting new cases to GCCR. The dataset included the clinical site, equivalent to the city of the cancer center, date of diagnosis and diagnosis, sex, age, presence of metastases at diagnosis, and onset of symptoms prior to cancer diagnosis (time-to-diagnosis, TTD). Reported diagnoses of pediatric malignancies were classified into 12 diagnostic groups according to the International Classification of Childhood Cancer, Third Edition (ICCC-3) by the authors.[19] 'Presence of metastases at diagnosis' was used as an approximation for disease stage (non-metastatic cases = early stage, metastatic cases = late stage), as due to various entities in the study population, definition of disease stage across all pediatric malignancies is difficult. This data was collected in the form of Yes/No for all solid tumors (diagnostic groups 3–12) and lymphoma, if applicable. One site did not report data on metastases and was therefore excluded from disease stage analysis. TTD described the time between the onset of symptoms and the definitive diagnosis of pediatric malignancy reported from medical history. For diagnoses without prior symptoms, prenatal diagnoses, and diagnoses at birth, TTD was coded as zero. For a reported period, e.g. 5–6 weeks, the middle of the period was chosen. For LMU Munich, one large center that constitutes a representative sample of the entirety of all, clinical sites in Bavaria, outpatient contacts of the pediatric emergency room (pER) were additionally analyzed for 2016–2021.

SARS-CoV-2 related data

Official Bavarian SARS-CoV-2 reports from the Bavarian Health and Food Safety Authority (LGL) were analyzed from the occurrence of the first SARS-CoV-2 infection in Bavaria (28-January-2020) until 31-December-2021. For the calculation of incidences, demographic data of the Bavarian population was downloaded from the Bavarian State Office for Statistics.[20] For 2016–2019, pediatric cancer incidences were calculated by the authors using the corresponding population estimates for children (0–17 years). The authors used the overall population of Bavaria in 2020 and 2021 to calculate SARS-CoV-2 specific incidences for both years 2020 and 2021 on a weekly basis and Bavarian children's population to calculate SARS-CoV-2 incidence for children in a similar manner.

Data on pandemic measures in Bavaria were obtained from the Healthcare Data Platform (previously Corona Data Platform).[21] In the data, individual restrictions were listed each day as in-/active according to the regulation in force at the time, missing data was imputed: if there were one or more ordinances without the specific code of the measure between two dates on which the same specific measure was coded as in-/active, the continuation of the specific measure was implied for these gaps and filled with the same value. Data on active measures regarding curfews and contact restrictions in private spaces were analyzed. 'Curfew' refers to restrictions regarding isolation, both day and/or night. Measures that included only recommendations were not considered.

Stringency indices (SI) served as measures of how strict infection control measures were. The indices are methodologically based on the Oxford Stringency Index.[22] SI for all pandemic restrictions and for restrictions in daycare, primary, and secondary schools were downloaded from the Healthcare Data Platform[21] for Bavaria from 01-March-2020 to 31-December-2021. For our analysis, SI for daycare/school restrictions was created by averaging available SI for daycare, primary, and secondary schools.

Statistical analysis

Age and TTD as continuous variables were summarized by median and interquartile range (IQR). Categorical data (number of childhood cancer diagnoses per diagnostic group and/or year, sex) were summarized by frequency and percentages. Differences among two groups of continuous data (TTD) were analyzed by Mann–Whitney *U*-test, between two groups of categorical variables (distribution of cancer diagnosis between 2016–2019 and 2020/2016–2019 and 2021) by means of Fisher's exact test. Temporal trends of incidence and TTD were analyzed by simple linear regression. Differences in the number of emergency room contacts in 2016–2019 and 2020 and 2021 were assessed using a chi-square test with a probability of 0.5 for the number of observed visits in both times, respectively. Similarly, we tested for differences in the monthly number of cancer diagnoses.

To assess the impact of the pandemic on the incidence of pediatric diagnoses, monthly incidence rate ratios (IRR) were calculated as the ratio between the incidence rate of childhood cancer in 2020–2021 and the mean incidence rate of childhood cancer in 2016–2019. 95%-confidence intervals for IRR as well as p-values were obtained from the *rateratio* function of the R package *epitools*. In the same fashion, the IRR of non-/metastatic cancer diagnoses were calculated to assess the impact of the pandemic on the disease stage at diagnosis.

The association between SARS-CoV-2 and childhood cancer incidences was investigated by calculating the cross-correlation between the time series of weekly SARS-CoV-2 and weekly childhood cancer incidences 2020–2021. To assess whether SARS-CoV-2 specific restrictions had an impact on childhood cancer incidence, cross-correlation between SI (overall and daycare/schools) and cancer incidence in children was additionally calculated. Cross-correlation analysis is described in detail in the supplementary methods.

Statistical analyses were carried out using the software R (Version 3.6.3) and GraphPad Prism 10. p-values <0.05 were considered significant. All analyses were explorative and no adjustments for multiple comparisons were considered.

Results

Study population

During the study period, 2350 children ($0 < 18$ years) were diagnosed with cancer. The median age of patients was 7.0 years with a slightly higher male preponderance of 55% in a ratio of 1.2. Leukemias were diagnosed most frequently (26.2%), followed by CNS tumors (24.4%), and lymphomas (13.9%). During the pandemic, frequency and distribution among diagnostic groups did not noticeably vary ($p = 0.999$ for 2016–2019 vs. 2020 and 2016–2019 vs. 2021). Patient characteristics are summarized in Table 1.

Diagnoses of pediatric malignancies

Monthly numbers of newly diagnosed pediatric malignancies in Bavaria 2020–2021 were compared to the average monthly numbers, minimum, and maximum in 2016–2019. No overall increase/decrease in pediatric malignancies was associated with the SARS-CoV-2 pandemic, but during the first year of the pandemic and into 2021, diagnoses slightly, but insignificantly exceeded average diagnoses from pre-pandemic years after a significant decrease in May 2020 ($p = 0.046$). Fluctuation was averaged over both pandemic years by a slight, but insignificant decrease in diagnoses in the second half of 2021 after a significant decrease in May 2021 ($p = 0.021$) (Figure 1a). The same pattern including significantly decreased diagnoses in May 2021 ($p = 0.004$) was observed for solid tumors (Figure 1b). For hematological diseases, i.e. leukemias and lymphomas, the pattern was similar, but no significant changes were detected (Figure 1c). For different age groups (toddlers <4 years, children <13 years, and adolescents <18 years) and urbanity of the clinical sites, changes in monthly numbers of cases also showed a similar course (Supplementary Figure 1a–f). No temporal trends were observed in the number of cancer diagnoses during the observation period (Supplementary Figure 2a).

Table 1. Patient characteristics, including age, sex, and frequency of diagnoses according to diagnostic group, prior and during the COVID-19 pandemic.

	Frequency (n (%))							Median age in years (IQR)	Male sex (n (%))
Diagnostic group*	Total	2016	2017	2018	2019	2020	2021		
Leukemias	616 (26.2%)	101 (33.7%)	96 (26.6%)	104 (28.0%)	103 (26.8%)	114 (26.6%)	98 (25.9%)	5.0 (5.0-10.0)	360 (58.4%)
Lymphomas	326 (13.9%)	55 (12.9%)	57 (15.8%)	51 (13.7%)	57 (14.8%)	55 (12.8%)	51 (13.5%)	13.0 (7.0-16.0)	229 (70.2%)
CNS and miscellaneous intracranial and intraspinal neoplasms	573 (24.4%)	121 (28.3%)	94 (26.0%)	90 (24.3%)	85 (22.1%)	94 (21.9%)	89 (23.5%)	7.0 (3.0-12.0)	304 (53.1%)
Neuroblastoma and other peripheral nervous cell tumors	126 (5.4%)	21 (4.9%)	20 (5.5%)	28 (7.5%)	16 (4.2%)	22 (5.1%)	19 (5.0%)	1.0 (0.3-3.0)	71 (56.3%)
Retinoblastoma	9 (0.4%)	4 (0.9%)	1 (0.3%)	0 (0.0%)	2 (0.5%)	0 (0.0%)	2 (0.5%)	1.0 (1.0-1.0)	5 (55.6%)
Renal tumors	96 (4.1%)	13 (3.0%)	20 (5.5%)	17 (4.6%)	16 (4.2%)	17 (4.0%)	13 (3.4%)	3.0 (1.0-5.0)	44 (45.8%)
Hepatic tumors	26 (1.1%)	6 (1.4%)	1 (0.3%)	7 (1.9%)	2 (0.5%)	6 (1.4%)	4 (1.1%)	1.5 (0.8-4.5)	17 (65.4%)
Malignant bone tumors	129 (5.5%)	26 (6.1%)	17 (4.7%)	22 (5.9%)	24 (6.3%)	26 (6.1%)	14 (3.7%)	12.0 (9.0-15.0)	72 (55.8%)
Soft tissue and other extraosseous sarcomas	99 (4.2%)	16 (3.7%)	16 (4.4%)	11 (3.0%)	24 (6.3%)	15 (3.5%)	17 (4.5%)	6.0 (2.0-13.0)	62 (62.6%)
Germ cell tumors, trophoblastic tumors, and neoplasms of gonads	136 (5.8%)	28 (6.6%)	8 (2.2%)	19 (5.1%)	21 (5.5%)	32 (7.5%)	28 (7.4%)	9.0 (1.0-14.0)	41 (30.1%)
Other malignant epithelial neoplasms and malignant melanomas	57 (2.4%)	6 (1.4%)	12 (3.3%)	7 (1.9%)	9 (2.3%)	14 (3.3%)	9 (2.4%)	13.0 (9.0-15.0)	26 (45.6%)
Other and unspecified malignant neoplasms	157 (6.7%)	30 (7.0%)	19 (5.3%)	15 (4.0%)	25 (6.5%)	34 (7.9%)	34 (9.0%)	7.0 (1.0-13.0)	64 (40.8%)
Total	2350	427	361	371	384	429	378	7.0 (2.0-13.0)	**1295 (55.1%)**

*Diagnostic groups are classified into 12 major diagnostic groups according to the International Classification of Childhood Cancer, Third Edition (ICCC-3).[19]

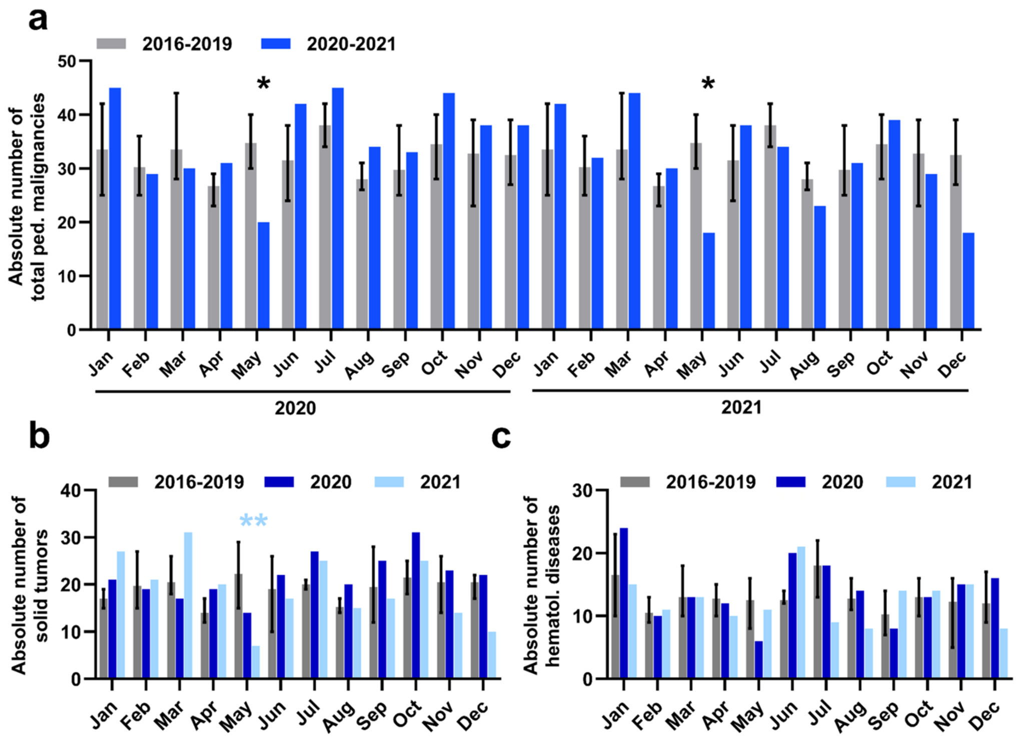

Figure 1. Diagnoses of pediatric malignancies during the pandemic.
Average number of newly diagnosed pediatric malignancies in the years 2016–2019 vs. absolute numbers of new diagnoses in 2020 and 2021 by calendar month. The whiskers represent the respective minimum and maximum number of cases diagnosed in that month in 2016–2019. The numbers are shown for all pediatric malignancies (a), and separately for solid tumors (b) and hematological diseases (c). Diagnostic groups were defined according to the International Classification of Childhood Cancer, Third Edition (ICCC-3), solid tumors include diagnostic groups 3-12. $*p < 0.05$, $**p < 0.01$.

SARS-CoV-2 pandemic proceedings

Weekly SARS-CoV-2 incidence/100,000 inhabitants in Bavaria was analyzed between January 2020 and December 2021, i.e. the first four COVID waves, in the general population and children (0–17 years) (Figure 2). While incidence in children was lower than in the general population at first, children showed higher infection incidence in the fourth wave. Periods of curfews, school closures, contact restrictions in private space, and restrictions in schools were first implemented during the first wave in March 2020 and eased near the end of infection wave one. The end of the first curfew coincided with the reopening of schools. Restrictions in private spaces and schools were tightened after the start of the second wave, incl. curfews and school closure, and only eased after the third wave. SI for daycare/school restrictions represent the proceedings of closure and restrictions in schools, overall SI shows the same trend in a weaker form (Figure 2). Pandemic phases in Germany and periods of restrictions implemented in Bavaria are retrieved from the Healthcare Data Platform and Epidemiological Bulletin 10/2022[21,23] and summarized in Table 2.

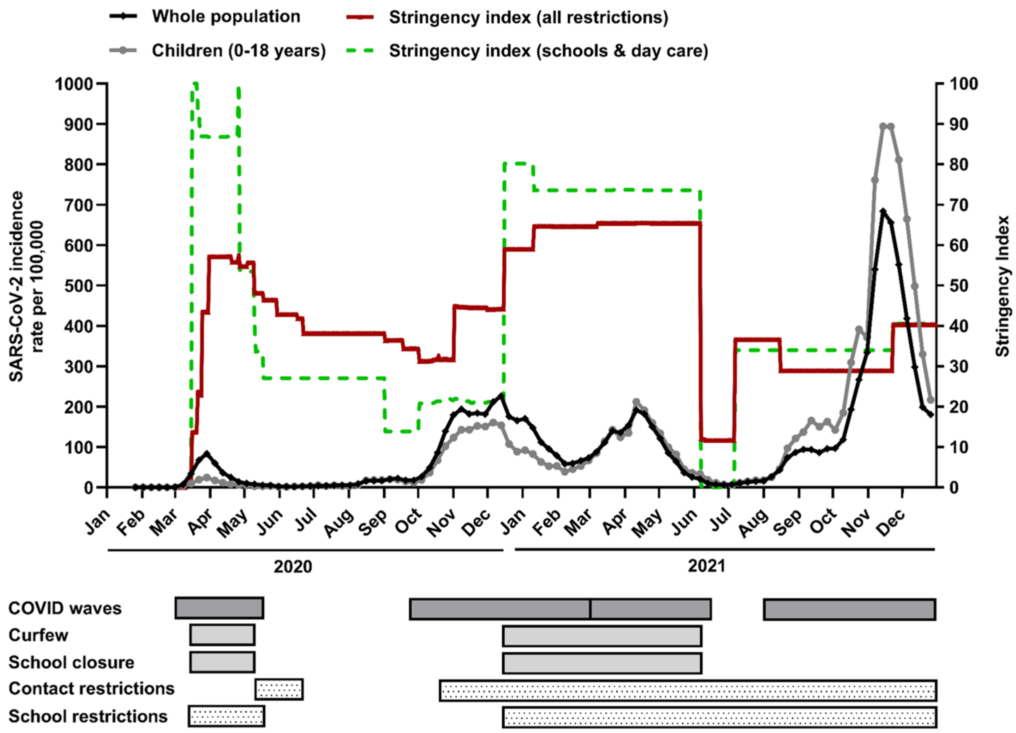

Figure 2. SARS-CoV-2 pandemic proceedings in Bavaria.
Weekly SARS-CoV-2 incidence per 100,000 inhabitants in Bavaria between January 2020 and December 2021 are shown for the general population and for children (0-18 years). The stringency index, a measure of how strict the infection control measures were overall, and a differentiated stringency index for school/daycare restrictions are plotted. Presented in blocks are COVID waves 1-4, curfews, restrictions in private space, and times of school closure and restrictions, as retrieved from the Healthcare Data Platform and Epidemiological Bulletin 10/2022.[21,23]

Table 2. SARS-CoV-2 pandemic in Germany. Pandemic phases and measures implemented in Bavaria during the first two years of the pandemic 2020-2021 as retrieved from the Healthcare Data Platform and Epidemiological Bulletin 10/2022.[21,34]

Pandemic phase	Start (calendar week)	End (calendar week)
Sporadic infections	5/2020	9/2020
First COVID wave	10/2020	20/2020
Summer plateau 2020	21/2020	39/2020
Second COVID wave	40/2020	08/2021
Third COVID wave	09/2021	23/2021
Summer plateau 2021	24/2021	30/2021
Fourth COVID wave	31/2021	51/2021*
Pandemic measures		
First school/daycare closure	12/2020	19/2020
First school restrictions	13/2020	20/2020
Second school/daycare closure	51/2020	22/2021
Second school restrictions	51/2020	52/2021**
First curfew	12/2020	19/2020
First contact restrictions in private space	20/2020	25/2020
Second contact restrictions in private space	43/2020	52/2021**
Second curfew	51/2020	18/2021[†]/22/2021[††]

*Fifth COVID wave started in KW 52/2021, **pandemic measures were active at the end of the observation period, [†]end of restrictions for fully vaccinated people or people that recovered from a SARS-CoV-2 infection, [††]end of restrictions for unvaccinated people.

Incidence fluctuation, disease stage, and TTD

IRR of pediatric malignancies significantly decreased in May of both pandemic years and December 2021: IRR = 0.57, 95%-CI: (0.33, 1.00), $p = 0.046$ for May 2020, IRR = 0.51, 95%-CI: (0.29, 0.91), $p = 0.019$ for May 2021, IRR = 0.55, 95%-CI: (0.31, 0.97), $p = 0.038$ for December 2021 (Figure 3a). New cases decreased by 42.4% in May 2020 and 48.2% in May 2021. During other months, no significant changes were detected.

Data on disease stage was available from five study sites for 1,277 patients (64.9%), as one clinical site did not report data on disease stage. Metastatic disease was diagnosed in 206 patients (10.5%). Monthly IRR of non-metastatic cases showed a similar pattern as total pediatric malignancies. We noted a statistically significant increase in IRR for March 2021 (IRR = 1.98, 95%-CI: (1.05, 3.72), $p = 0.031$) and a decrease in non-metastatic diagnoses in May 2021 (IRR = 0.31, 95%-CI: (0.11, 0.84), $p = 0.015$) (Figure 3b). No significant changes were noted during other months. For metastatic cases, a non-significant, but fourfold increase in diagnoses was seen in June-July 2020 and July 2021 (Figure 3c). In pre-pandemic years, the mean percentage of metastatic diseases among diagnoses in July was 3.2%, it increased to 9.8% in July 2020 and 14.3% in July 2021. Incidence of metastatic diseases appeared to be highest in summer; however, the corresponding IRR was not statistically significant (IRR = 4.00, 95%-CI: (0.45, 35.77), $p = 0.180$ for July 2020; IRR = 3.96, 95%-CI: (0.44, 35.39), $p = 0.184$ for July 2021). The excess of metastatic cases was not stronger in certain diagnostic groups than in others.

TTD was available for 1,822 patients (77.5%). The distribution of missing data was analyzed regarding their distribution among age and diagnostic groups, sex, diagnosed year, and clinical sites. No accumulation in certain subgroups was apparent. Median TTD in 2016–2019 was 3.0 wks (IQR: 1.0–8.7) and 4.0 wks in 2020–2021 (IQR: 1.3–9.7) (Figure 3d). This difference was statistically significant with $p = 0.037$. Among different types of cancer, TTD was statistically prolonged during the pandemic for solid tumors ($p = 0.039$) (Supplementary Figure 3a). TTD was prolonged in all age groups (toddlers 0–3 years, children 4–12 years, and adolescents 13–17 years), but no significant differences were detected (Supplementary Figure 3b), and for medium and large cities, with a significant increase for medium cities (Supplementary Figure 3c). No temporal trends were observed in TTD during the observation period (Supplementary Figure 2b).

The mean outpatient contacts of pER at LMU Munich were 10,483 in 2016–2019. Contacts during the pandemic were significantly lower (2020: $n = 5{,}877$, $p < 0.001$; 2021: $n = 7138$, $p < 0.001$) (Figure 3e).

Cross-correlation

No statistically significant association was found between SARS-CoV-2 incidence and childhood cancer incidence (correlation at lag 0: −0.06, 95%-CI: (-0.26, 0.14) for SARS-CoV-2 incidence in the whole population, correlation at lag 0: −0.12, 95%-CI: (-0.32, 0.08) for children of 0–17 years, Supplementary Figure 4a). A weak, yet statistically significant association was found between overall SI and childhood cancer incidence, where childhood cancer incidence follows SI with a time delay of 3–6 wks

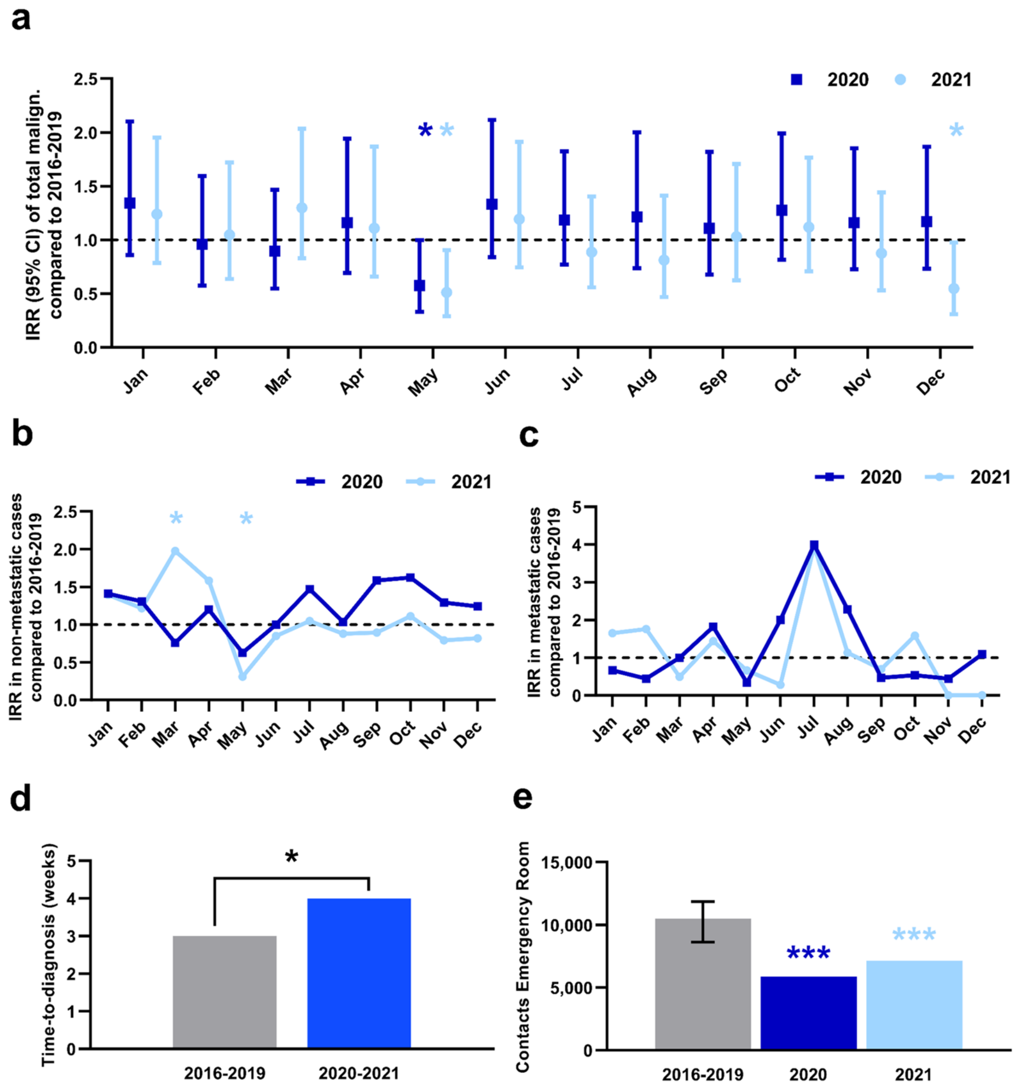

Figure 3. Change in incidence, stage, and time-to-diagnosis (TTD) of pediatric malignancies during the SARS-CoV-2 pandemic.

Incidence Rate Ratios (IRR) during the pandemic years 2020 and 2021 compared to the pre-pandemic years 2016-2019 are shown per calendar month for all pediatric malignancies including 95%-CI (a). IRR is shown for cases diagnosed without metastases at the time of diagnosis (b), and cases with present metastases at diagnosis (c). Median TTD (d) and outpatient contacts of the pediatric emergency room at LMU Munich (e) are shown for the pre-pandemic years 2016-2019 and during the pandemic years 2020-2021. The whiskers represent the respective minimum and maximum number of outpatient contacts in 2016-2019, *$p < 0.05$, ***$p < 0.001$.

(Supplementary Figure 4b). These correlations are low (maximum correlation of 0.26, 95%-CI: (0.06, 0.45) for the 5-week delay), but may imply a positive correlation between the two time series, i.e. an increase in childhood cancer incidence following an increased SI. We also found a statistically significant association between SARS-CoV-2 incidence and SI with a maximum correlation of −0.31, 95%-CI: (−0.51, −0.11) after a delay of 12 wks (significant range: 6–16 wks, Supplementary Figure 4c). This is interpreted as a decrease in SARS-CoV-2 incidence after an increase in SI or an increase in SARS-CoV-2 incidence after a decrease in SI with a time lag of 6 to 16 wks.

Discussion

In order to address the remaining concerns for (indirect) impact of the COVID-19 pandemic on the healthcare system and to identify vulnerable steps in children's medical care during the pandemic, we describe a distinct and complete regional dataset of pediatric malignancies, which represents childhood cancer characteristics in Germany,[24] and SARS-CoV-2 pandemic proceedings during the years most affected by the pandemic. We found that regional cancer diagnoses showed a deficit of cases in May and thereafter an excess from June to the end of the year 2020 and early 2021 across diagnostic groups. This corresponds to evidence from GCCR[17] and the overall increasing trend reported for Germany.[25] For the second half of 2021 we observed fewer cases than for 2020, especially in December, where IRR decreased. Late reporting needs to be considered and interpretation of changes remains speculative, but nevertheless, the findings match the data from GCCR who observed a rebound effect from increased diagnoses (2020) in 2021 for some diagnostic groups.[18] Albeit the strong impact on patient care and availability of medical consultations for in-patient and out-patient care of adults, pediatrics did not appear to be affected much by the COVID-19 pandemic.[17] In the contrary, fewer and shorter hospitalizations were reported in 2020 e.g. for pediatric patients with type 1 diabetes in Bavaria.[26]

We observe a significant decrease in newly diagnosed pediatric malignancies in May (2020: −42.4%, 2021: −48.2%). The decrease in May 2020 is timely associated with the aftereffect of the first SARS-CoV-2 wave in Germany, which started in March, and the first implication of pandemic restrictions that were active until the end of May. The decrease in cancer diagnoses in May 2021 was also timely associated with a spring wave of SARS-CoV-2 and consecutive restrictions, however, this association is less clear. Even though it seems that the pandemic did not severely impact medical care accessibility for children, findings have been published that the start of the pandemic created fear in society leading to decreases in quality of life and physical as well as psychological health.[27] Decreased diagnoses may also be interpreted as higher fluctuation due to ever-changing restrictions resulting in hospital avoidance, or elimination of vaccination prioritization in spring 2021, which in return may have nurtured hospital avoidance.

Reduced pER contacts have been reported and assessments concluded parental hospital avoidance due to fear and uncertainty as well as misinterpretation of governmental advice.[6,28,29] We confirmed with data from one large children's hospital that constitutes a representative sample of the entirety of clinical sites in Bavaria, significantly less outpatient pER contacts during the pandemic, although the availability of consultations remained the same. From this finding we may hypothesize that the main impact of the pandemic was not on a structural level, i.e. leading to capacity problems or delays in treatment starts, but rather the absence of patients in the hospitals, despite accessibility and availability of outpatient slots.

Correlation analysis between pediatric cancer incidences and overall SI resulted in a weak, but statistically significant correlation with a temporal delay of 3–6 wks during the pandemic. This could potentially translate to avoidance of unscheduled consultation after restrictions were tightened. Altogether, our data support the assumption that the behavior of families was negatively influenced, especially during peaks of the pandemic, leading to avoidance of contact to medical care and thus indirectly influencing the incidence of newly diagnosed pediatric malignancies.

Following significantly decreased diagnoses in May 2020/2021, we observed an increase in metastatic diagnoses two months later, even though this finding was statistically insignificant. Delayed diagnoses from spring may have resulted in an advanced disease stage for new diagnoses in summer. In our data we noted significantly prolonged TTD during the pandemic, further supporting our hypothesis of delayed medical consultation. Even though only a few data have been reported so far to make conclusions about the consequence of a prolonged diagnostic interval in childhood cancer, a recent systematic review and meta-analysis described increased mortality across cancer entities by a four-week delay of cancer treatment in adults.[30] Relations between delay in diagnosis and outcome are complex and TTD varies between entities and with age,[31] but with prolonged TTD disease may progress and can negatively influence prognosis in most malignancies.[32,33] Thus, we assume that late diagnosis could lead to a worse prognosis in at least a subset of patients, and timely diagnosis should remain the goal for pediatric cancer patients.[34]

This study covers a geographically small region and the major years of the pandemic. The data set has the advantage of deriving from a conserved region with uniform pandemic proceedings and including complete cancer incidence, thus reliably reflecting the situation. A limitation concerns missing data regarding TTD and disease stages. Distribution of missing data was assessed and no concerns regarding systematic underreporting or increased reporting during the pandemic were raised. There is an uncertain number of additional cases diagnosed in 2021 that were only recorded after February 2022 when data for this study was received. However, data was recently published confirming slightly decreased diagnoses in the latter half of 2021, confirming our findings.[18] Due to the exploratory nature of our study and without p-value adjustments, we cannot exclude the possibility that some statistically significant associations were due to chance. However, our intention was not to focus on p-values but to describe the changes in the data that we saw.

Conclusion

We describe a distinct and complete regional dataset of pediatric malignancies and SARS-CoV-2 incidence during the major phase of the pandemic. From our findings, we may hypothesize that there have been effects on pediatric cancer diagnosis during the COVID-19 pandemic at vulnerable times that may have led to hospital avoidance and delays in diagnosis. Interpretation of these changes remains speculative with potential causes being behavior patterns such as hesitation and concerns, and potential societal changes during phases of public restrictions, rather than overwhelmed medical capacities. Further studies are needed to capture the complete effects of the pandemic on pediatric cancer care throughout the pandemic. They should include geographical and socio-economic information on the patient population, assessment of surveillance limitations, and analyses of overall and progression-free survival to also capture potential late effects with the aim to raise specific awareness and prevent delay in children's medical care during potential future pandemics.

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Authors' contribution

MR and KM performed data analysis and visualization. MR prepared the manuscript draft. MR, KM, and TF contributed to the research design and reviewed the manuscript. All authors provided data, contributed to the interpretation of the data, reviewed, and approved the final manuscript.

Disclosure statement

The authors declare no competing interests.

Ethics statement

The Institutional Ethical Review Board approved this study (reference 21-0732). Due to the strictly retrospective analysis and the anonymization of patient data, an informed consent form for individual participants was not required.

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Data availability statement

SARS-CoV-2 data is available at the Bavarian Health and Food Safety Authority (LGL), and data regarding pandemic measures in Bavaria can be downloaded from the Healthcare Data Platform.[21]

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