Comparison of pneumonia features in children caused by SARS-CoV-2 and other viral respiratory pathogens.

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Abstract

Pneumonia is a frequent manifestation of COVID-19 in hospitalized children. Methods The study involved 80 hospitals in the SARS-CoV-2 Spanish Pediatric National Cohort. Participants were children <18 years, hospitalized with SARS-CoV-2 community-acquired pneumonia (CAP). We compared the clinical characteristics of SARS-CoV-2-associated CAP with CAP due to other viral etiologies from 2012 to 2019. Results In total, 151 children with SARS-CoV-2-associated CAP and 138 with other viral CAP included. Main clinical features of SARS-CoV-2-associated CAP were cough 117/151(77%), fever 115/151(76%) and dyspnea 63/151(46%); 22/151(15%) patients were admitted to a pediatric intensive care unit (PICU), and 5/151(3%) patients died. Lymphopenia was found in 63/147(43%) patients. Chest X-ray revealed condensation (64/151[42%]) and other infiltrates (87/151[58%]). Compared with CAP from other viral pathogens, COVID-19 patients were older (8 vs.1 year; odds ratio [OR] 1.42 [95% confidence interval, CI 1.23;1.42]), with lower CRP levels (23 vs.48 mg/L; OR 1 [95%CI 0.99;1]), less

wheezing (17 vs.53%; OR 0.18 [95%CI 0.11;0.31]) and greater need of mechanical ventilation, MV (7 vs.0.7%, OR 10.8 [95%CI 1.3;85). Patients with non-SARS-CoV-2-associated CAP had a greater need for oxygen therapy (77 vs.44%, OR 0.24 [95%CI 0.14;0.40]). There were no differences in the use of CPAP or HVF or PICU admission between groups. Conclusion SARS-CoV-2-associated CAP in children presents differently to other virus-associated CAP: children are older and rarely have wheezing or high CRP levels; they need less oxygen but more CPAP or MV. However, several features overlap, and differentiating the etiology may be difficult. The overall prognosis is good.

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Potential conflicts of interest

No conflicts of interest.

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ABSTRACTPneumonia is a frequent manifestation of COVID-19 in hospitalized children. **Methods** The study involved 80 hospitals in the SARS-CoV-2 Spanish Pediatric National Cohort. Participants were children <18 years, hospitalized with SARS-CoV-2 community-acquired pneumonia (CAP). We compared the clinical characteristics of SARS-CoV-2-associated CAP with CAP due to other viral etiologies from 2012 to 2019.

Results In total, 151 children with SARS-CoV-2-associated CAP and 138 with other viral CAP included. Main clinical features of SARS-CoV-2-associated CAP were cough 117/151(77%), fever 115/151(76%) and dyspnea 63/151(46%); 22/151(15%) patients were admitted to a pediatric intensive care unit (PICU), and 5/151(3%) patients died. Lymphopenia was found in 63/147(43%) patients. Chest X-ray revealed condensation (64/151[42%]) and other infiltrates (87/151[58%]). Compared with CAP from other viral pathogens, COVID-19 patients were older (8 vs.1 year; odds ratio [OR] 1.42 [95% confidence interval, CI 1.23;1.42]), with lower CRP levels (23 vs.48 mg/L; OR 1 [95%CI 0.99;1]), less wheezing (17 vs.53%; OR 0.18 [95%CI 0.11;0.31]) and greater need of mechanical ventilation, MV (7 vs.0.7%, OR 10.8 [95%CI 1.3;85). Patients with non-SARS-CoV-2-associated CAP had a greater need for oxygen therapy (77 vs.44%, OR 0.24 [95%CI 0.14;0.40]). There were no differences in the use of CPAP or HVF or PICU admission between groups.

Conclusion SARS-CoV-2-associated CAP in children presents differently to other virus-associated CAP: children are older and rarely have wheezing or high CRP levels; they need less oxygen but more CPAP or MV. However, several features overlap, and differentiating the etiology may be difficult. The overall prognosis is good.

INTRODUCTION

Community-acquired pneumonia (CAP) is one of the most frequent infectious diseases in children, leading to widespread antibiotic use and hospitalization. While CAP is often multifactorial, viruses, including respiratory syncytial virus (RSV), human metapneumovirus (hMPV), influenza, parainfluenza virus (PIV), rhinovirus (RhV) and adenovirus (ADV), are considered as the main causative agents of pediatric CAP worldwide, with a reported rate of 25% to 82%[1–4].

Like other viruses of the coronavirus family, SARS-CoV-2 causes a spectrum of clinical manifestations grouped under the term coronavirus disease 2019 (COVID-19), and patients often present with respiratory con-

ditions of different severity, including CAP. Children usually have a less severe COVID-19 infection than adults[2-9], and <15% require hospitalization[5–8]. Among hospitalized children, however, the most frequent diagnosis is CAP.

We recently showed that COVID-19 positivity by real-time PCR (RT-PCR) in children can persist for up to three months[9]. Accordingly, a positive PCR in a child with non-SARS-CoV-2 viral CAP can be misdiagnosed as COVID-19. It remains unclear whether SARS-CoV-2-associated CAP can be differentiated from other viral CAP-related infections based on clinical, analytical or radiographical findings. In addition, in children with CAP and coinfections with SARS-CoV-2 and other viruses, it is difficult to distinguish which virus contributes most to the CAP[10].

The present study sought to determine the characteristics of children admitted due to SARS-CoV-2-associated CAP and to compare these findings with those of children with other viral-associated CAP.

MATERIALS AND METHODS

Patients.

The Epidemiological Study of Coronavirus in Children (EPICO-AEP) is a prospective multicenter national study conducted in Spain to assess the characteristics of children with COVID-19. In the present study, we included hospitalized children with a primary diagnosis of SARS-CoV-2-associated pneumonia enrolled in EPICO-AEP. CAP was defined as fever or respiratory symptoms and an image consistent with pneumonia in the chest x-ray, according to the criteria applied by the attending physician. COVID-19 infection was confirmed by RT-PCR testing or by rapid antigen detection testing on nasopharyngeal swabs. We enrolled pediatric patients (ages 18 years and younger) from 80 hospitals of the network, from February 25$^{\text{th}}$, 2020 to April 30$^{\text{th}}$, 2021.

Epidemiological, clinical, laboratory and radiological data were collected from medical records, including the age at onset of the infection, sex, clinical signs and symptoms, outcomes, laboratory data, chest X-ray findings, comorbidities, treatment, and pediatric intensive care unit (PICU) admission. Radiographs were obtained following the institutional protocols of each participating center, and all included patients underwent at least one chest X-ray. We used a standardized data collection online platform (Research Electronic Data Capture: RedCAP$^{\text{TM}}$) to record and collect the clinical data.

The findings were compared with data from children diagnosed with viral-associated CAP from a different study performed by our group[11]. In this study, eligible participants were children under 18 years of age admitted to any of the participating hospitals, with radiologically-confirmed CAP, from April 2012 to May 2019. An extensive microbiological workup was performed, including blood cultures, *Streptococcus pneumoniae* antigen (BinaxNow$^{\text{TM}}$) and/or RT-PCR for *S.pneumoniae* in pleural fluid if thoracentesis was performed, RT-PCR in blood for*S.pneumoniae* , multiplex RT-PCR on nasopharyngeal aspirate samples for pertussis and for the following panel of 16 viruses: RSV, hMPV, PIV 1, 2, 3 and 4, influenza (A and B), human bocavirus (hBoV), ADV, enterovirus (EV), RhV, and coronavirus (CoV) 229E, OC43, NL63 and HKU12. Two paired samples for serology (at admission and 2–4 weeks later) for*Mycoplasma pneumoniae* and *Chlamydia pneumoniae* were performed using enzyme-linked immunoassays [12].

Viral etiology was assigned to CAP if at least one putative pathogen respiratory virus (RSV, influenza A or B, PIV, hMPV) was detected in nasopharyngeal aspirates by PCR, and no bacterial pathogen was detected. Other respiratory viruses (RhV, ADV, EV, CoV, hBoV) were not included as likely viral infections due to poor specificity for CAP[13,14].

Both studies were approved by the ethics committee of every center, and all guardians signed the informed consent to participate in the study.

Statistical analysis.

Data were described with frequencies for categorical variables and means (SD) or medians (interquartile range [IQR]) for continuous variables (depending on normal or non-normal distribution), both in the total

population and stratified by type of pneumonia (Table 1). χ^2 or Fisher's tests were applied to assess differences across groups for categorical variables, and Student's t test or the Mann–Whitney U test was used for continuous variables. Two-tailed $p<0.05$ was considered statistically significant.

Univariable comparisons were segmented by the presence (Yes) or absence (No) of patients' features among children with SARS-CoV-2 CAP and other viral CAP. We also performed univariate comparisons for different outcome endpoints (admission to PICU, complications, etc., to test for differences between patients with COVID-19 CAP or other virus-associated CAP. The latter analysis consisted of stepwise multivariable binary logistic regression, with the endpoint being PICU admission (Table 2). The multivariable model was adjusted by type of pneumonia, sex, age (years), asthma, respiratory rate, oxygen saturation, wheezing, shortness of breath or work breathing, radiological image interpretation, leukocytes, C-reactive protein (CRP), neutrophils, lymphocytes, sodium, albumin, procalcitonin and hemoglobin. The optimum model was selected according to Akaike Information Criteria (AIC).

REDCap data were exported to the R language (4.0.3)[15]for analysis. R packages were used for specific analysis, such as compare Groups (4.4.6) for comparisons or MASS (7.3.53)[16] for stepwise logistic regression.

RESULTS

As of April 30th, 2021, the EPICO-AEP database had registered 666 hospitalized patients, including 165/666 (25%) with a final diagnosis of CAP at discharge. Of the 165 patients, 151 with pathological chest X-ray (CXR) on admission were selected for the comparative study. The participants included 91/151 (60%) male children, with a median age of 8 years (IQR 1–13). A total of 76/151 (50%) children had household contact with a confirmed COVID-19 patient.

For analytical purposes, the patients were distributed according to the COVID-19 waves. Until the end of April 2021, Spain experienced four waves (Figure 1): 1st wave, February 27th to May 31st, 2020; 2nd wave, June 1st to November 2nd, 2020; 3rd wave, September 15th to December 15th, 2020; 4th wave, December 15th, 2020 to April 30th, 2021. The maximum peak of admissions for CAP was recorded during the first wave: with 83% of cases (126/151).

Clinical features and outcomes of patients with SARS-CoV-2-associated pneumonia.

Demographic, clinical, analytical, and radiological characteristics are shown in Table 1. Almost half (72/151, 48%) of all children in our series had underlying conditions, including: asthma, 29/144 (20%); immunosuppressive treatment, 22/151 (14%); chronic lung disease, 16/151 (11%); or heart disease, 15/151 (10%). Most children had fever 115/151 (76%) or cough 117/151 (77%) at admission, and 63/151 (42%) had dyspnea or work of breathing. Other features included rhinorrhea 61/151 (40%) or fatigue 40/151 (26%), and only 5/151 children (3%) had anosmia or dysgeusia. Of the 151 patients, 22 (15%) required admission to a PICU, during a median of 5 days (IQR 1–15). Most children (146/151, 97%) had a favorable clinical course and were discharged after improvement. However, 5/151 (3%) children died, and all had serious comorbidities: 3 had chronic lung disease (bronchopulmonary dysplasia, idiopathic interstitial pneumonia or pulmonary pathology due to spinal muscular atrophy), and 2 had immunosuppression due to hematological disease and bone marrow transplant.

Radiology and laboratory findings .

For the diagnosis of pneumonia, all patients underwent at least one chest X-ray. Upon admission, 151 patients presented with initial CXR alterations, with 64/151 (42%) presenting with consolidation and 87/151 (58%) showing other infiltrates, according to WHO classification. Only a few patients (6/151, 4%) presented with pleural effusion and in 4 of them (67%) thoracentesis was performed. Coinfection was demonstrated in only 5/151 (3%) cases: two cases of *Staphylococcus aureus* , one of *S.pneumoniae* (pneumococcal antigen in pleural fluid), and two due to rhinovirus and influenza virus (1/151, 0.6% each).

Full blood count (FBC) analysis revealed leukopenia ($<5 \times 10^9$/L) in 41/142 (29%) cases, lymphocytopenia ($<1.5 \times 10^9$/L) in 59/142 (42%), thrombocytopenia ($<150 \times 10^9$/L) in 22/142 (15%) and anemia (hemo-

globin <11.5 g/L) in 54/142 (38%) cases. Regarding inflammatory markers, CRP levels >20 mg/L were reported in 65/135 (48%) patients, and procalcitonin levels >0.5 ng/ml in 26/102 (25%), with 12/102 (12%) of the patients having levels >2 ng/ml. Regarding blood coagulation function, the D-dimer median was 699.5 µg/L (IQR 160.5–3402) and was increased in 62/96 (65%) of the patients. Other findings are shown in Table 1.

Evolution and treatment.

During the admission, 67/151 (44%) patients required oxygen therapy, during a median of 4 days (IQR 2–28). Regarding respiratory support, 15/151 (10%) required high-flow ventilation (HFV) or continuous positive airway pressure (CPAP); 11/151 (7%) required intubation and mechanical ventilation (MV) during a median of 5 days (IQR 2–16), and 2/151 (1%) required extracorporeal membrane oxygenation therapy.

Overall, 112/151 (74%) patients received antibiotics, mainly, azithromycin (55/112, 49%), ceftriaxone (27/112, 24%), ampicillin (5/112, 4%) or meropenem (6/112, 5%). Antivirals were administered to 67/151 (44%) patients; the most common were remdesivir (12/67, 18%) and lopinavir/ritonavir (10/67, 15%). Other treatments used were hydroxychloroquine in 52/151 (34%) patients, and immunoglobulins (3/151, 2%) or glucocorticoids (30/151, 20%).

Comparison between SARS-CoV-2 and other viruses associated with pneumonia.

Unlike the group with SARS-CoV-2-associated CAP, no deaths occurred in the group of CAP caused by other viruses.

Compared with patients with other viral-associated CAP, patients with SARS-CoV-2-associated CAP were older (8 vs. 1 year; odds ratio [OR] 1.33 [95% confidence interval, CI 1.23;1.44], p<0.001), had lower CRP levels (22 vs. 48 mg/L; OR 1 [95%CI 0.99;1], p<0.001), with less wheezing (17 vs. 53%; OR 0.18 [95%CI 0.11;0.31], p<0.001) and less work of breathing (42 vs. 83%; OR 0.18 [95%CI 0.10;0.31], p<0.001) (Table 1). We found that SARS-CoV-2 CAP was associated with a longer duration of fever (5 vs. 4 days; OR 1.16 [95%CI 1.08;1.26], p<0.001) but lower grade fever (37.8 vs. 39ºC; OR 0.35 [95%CI 0.26;0.46], p<0.001), more chest pain (14 vs. 6%; OR 3.39 [95%CI 1.48;8.54], p 0.006) and more abdominal pain (11 vs. 4%; OR 3.17 [95%CI 1.24;9.23], p 0.024). Patients with SARS-CoV-2-associated CAP showed more infiltrates than in the other viral CAP group by CXR (58 vs 35%; OR 2.46 [95%CI 1.53;3.98], p<0.001).

Use of oxygen therapy was more frequent in the other viral CAP group (76.8 vs. 44%; OR: 0.24 [95%CI 0.14;0.40], p<0.001). Conversely, patients with COVID-19 had more cardiological complications, including myocardial dysfunction, shock or arrhythmia (16.6 vs. 8.7%, OR 2.08 [95%CI 1.01;4.3], p=0.049) and more need of MV (7 vs. 0.7%, OR 10.8 [95%CI 1.3,85), p=0.02). There were no differences in the use of CPAP or HVF (10 vs. 5.8%, OR 1.79 [95%CI 0.73 to 4.3], p=0.19) or PICU admission (15 vs 9%, OR, 1.78 [95%CI, 0.85;3.77], p=0.125).

The logistic regression model showed that PICU admission was more likely in patients with higher levels of sodium and in patients with prior asthma. Likewise, the odds of PICU admission increased as lymphocytes or hemoglobin decreased (Table 2, Figure 3).

DISCUSSION

In this study, we compared CAP in patients with SARS-CoV-2 with patients positive for other viral infections. We found that the former was associated with less wheezing and work of breathing, a significantly lower lymphocyte fraction and lower CRP levels. During evolution, the SARS-CoV-2-associated CAP group had significantly higher MV use (almost ten-fold) but less requirement for oxygen. No significant differences were found in terms of days of hospitalization, PICU admission or CPAP/HFV use.

Several studies have reviewed the characteristics of adults with SARS-CoV-2 and pneumonia[17–21], but these remain scarce in the pediatric population[22,23]. However, among hospitalized children and adolescents, pneumonia is a major cause of disease (approximately –gativizes after a median of 17-e PCR15%)[5–8].

Similar to other studies[22,23], the most frequent symptoms in our patients were fever, cough, wheezing or shortness of breath. We found that SARS-CoV-2-associated CAP occurred in older children (8 years on average, as reported previously[24]), with a longer duration of fever, more cases with chest and abdominal pain and fewer cases with cough, wheezing or dyspnea than in non-SARS-CoV-2-associated CAP. Symptoms often overlapped, making it challenging to discern between the two. Given that the median time to RT-PCR negativity for SARS-CoV-2 is 17–19 days, and can remain positive for several weeks up to 3 months[25,26], a means of differentiating SARS-CoV-2 from other etiologies is important.

Many studies evaluating the utility of biomarkers in defining the etiology of pediatric CAP have been performed using FBC, neutrophil percentage, serum CRP or procalcitonin, although the cut-off points are not well defined. As reported in other studies, we found significant differences in terms of FBC and inflammatory markers[6,22,23,27], with increased CRP in almost 50% of the patients, but less intense in the SARS-CoV-2 group than in the non-SARS-CoV-2 group. Some studies have reported very high rates of lymphocytopenia[6,23], but it appears to be less common in children than in adults[12,13]. Variable ymphocytopenia values have been found in children, between 3–33%[8,21,22,28,29]. In our cohort, 42% of the children presented with lymphocytopenia. Both leukocytes and lymphocytes were significantly lower in patients with SARS-CoV-2-associated CAP than in other viral-associated CAP.

The evolution in children was usually good. Mortality in children with SARS-CoV-2-associated CAP is rare, less than 5% in different series[7,23,30] (3% in our study). It seems that patients with comorbidities are at higher risk[23,30]: In this context, about 50% of the EPICO group had underlying conditions.

The radiological presentation of SARS-CoV-2 can be non-specific and indistinguishable from other pathologies. The first published studies of children reported few findings in radiographs[15]; however, subsequent reports have revealed a higher proportion of radiographic abnormalities[11], which depend on the severity of pulmonary involvement[31,32]. In adults, most computed tomography studies in SARS-CoV-2-associated CAP show ground-glass opacities (25–60% according to different studies)[33–38] that can progress to white lung. The proportion of white lung in children is low, and the mechanism is worth further study. Here, the proportion of other infiltrates was 58%, which might correspond to ground-glass opacities, but they did not often progress to white lung, perhaps because of the limited inflammatory response in children. The proportion of consolidations in SARS-CoV-2-associated CAP (42%) was lower than that found in the other viral CAP group (64%), and again the interpretation is unclear. It might reflect different possible patterns of the infection or different susceptibility to bacterial superinfection. Although bacterial coinfections are frequent in viral CAP[4,38,39], they were very rare in our cohort (2%). However, a full work-up was not performed for most patients (due to laboratory overload during the pandemic). In some severe cases, pleural effusion may be found but it is rare[10-11,34] (in our series we found it only in 6 patients, 4%).

Severe COVID-19 is rare in children, with variable PICU admission rates[22,23,30]. In our cohort, 15% of children with SARS-CoV-2-associated CAP required PICU admission and while this was almost double the proportion of the other viral CAP group, the differences were not significant, which may be due to a limited sample size.

Usually, viral-associated CAP in young infants resolves with oxygen therapy or CPAP. The evidence for an effective treatment for SARS-CoV-2 is evolving rapidly. Most reports mention supportive treatment[12], including oxygen therapy and MV, but MV requirements are highly variable according to different studies in adults (18–42%[40]). Approximately, half of all our COVID-19 patients required oxygen therapy, up to 10% needed additional noninvasive respiratory support (CPAP, HFV), and 15% required MV. In our cohort, patients with other viral-associated CAP required oxygen more frequently, but SARS-CoV-2-associated CAP had more complications with a greater use of MV. Lung damage associated with SARS-CoV-2 appears different to other viruses, as patients need oxygen less often and MV more often. We hypothesize that part of the respiratory damage is vascular, neuro-muscular, or heart-mediated, rather than solely hypoxemia.

Although a high percentage of patients (74%) in our series received antibiotic treatment, it is often not needed in SARS-CoV-2-associated pneumonia owing to the viral etiology. The reason for this high proportion might

lie in the fact that most of our cases were during the first wave of the pandemic when treatment was not yet well established, and by the high percentage of severe cases, as only hospitalized patients were included. Even so, most cases of viral-associated CAP receive antimicrobials at admission[11].

Our study has some limitations. First, only hospitalized patients were included, and so the results are not representative for ambulatory CAP. Second, some cases had incomplete documentation of the exposure history or clinical features, and not all patients underwent a complete blood test or microbiological workup. The third limitation is the variation in the interpretation of radiographs depending on the observer, which can lead to different interpretations. Likewise, both cohorts were not paired in time, which can complicate the comparability of the results.

CONCLUSIONS

SARS-CoV-2 CAP is associated with more use of advanced respiratory support than other viral-associated CAP, and is also related to lower leukocyte and lymphocyte counts, less wheezing or shortness of breath and lower CRP. Nevertheless, the overall prognosis is usually good. Although we found some significant differences, many clinical and analytical findings often overlapped. Given that PCR can remain positive for some weeks in children with a positive detection of SARS-CoV-2, we should not automatically exclude the possibility of other viral pathogens.

FIGURES AND TABLES

Figure 1. Monthly admissions of children with SARS-CoV-2-associated CAP

Figure 2. Forest plot of baseline features of patients' risk for SARS-CoV-2-associated CAP (stepwise multivariable binary logistic regression).

Figure 3. Forest plot for the SARS-CoV-2-associated CAP risk of complications (ref: other viral CAP). PICU: Pediatric intensive care unit. CPAP: Continuous positive airway pressure. HFV: High flow ventilation.

Table 1. Basal features and risk of SARS-CoV-2-associated CAP

Table 2. Stepwise multivariable binary logistic regression. Endpoint: Admission to Pediatric intensive care unit (PICU). The multivariable model was adjusted by type of pneumonia, sex, age in years, asthma, respiratory rate, oxygen saturation, wheezing, shortness of breath or work breathing, radiological image interpretation, leukocytes, C-reactive protein, neutrophils, lymphocytes, sodium, albumin, procalcitonin y hemoglobin. The optimal model was selected according to Akaike Information Criteria (AIC). Significance codes: *<0.05, **<0.01

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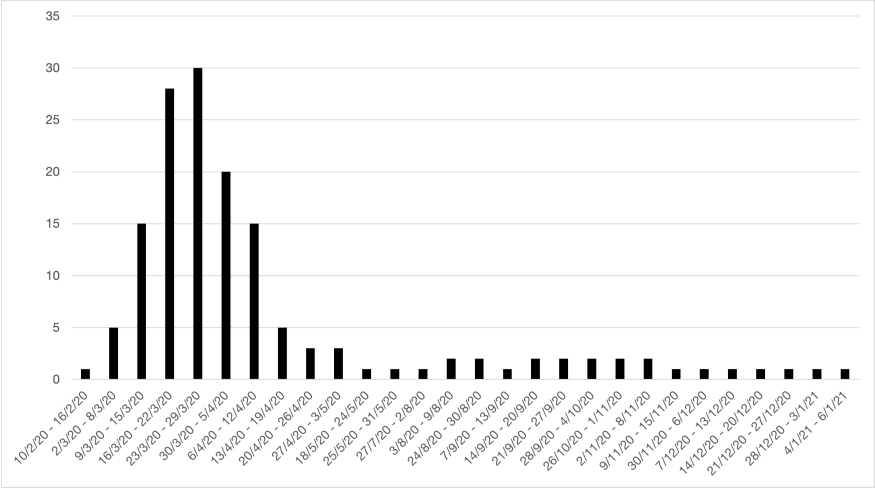

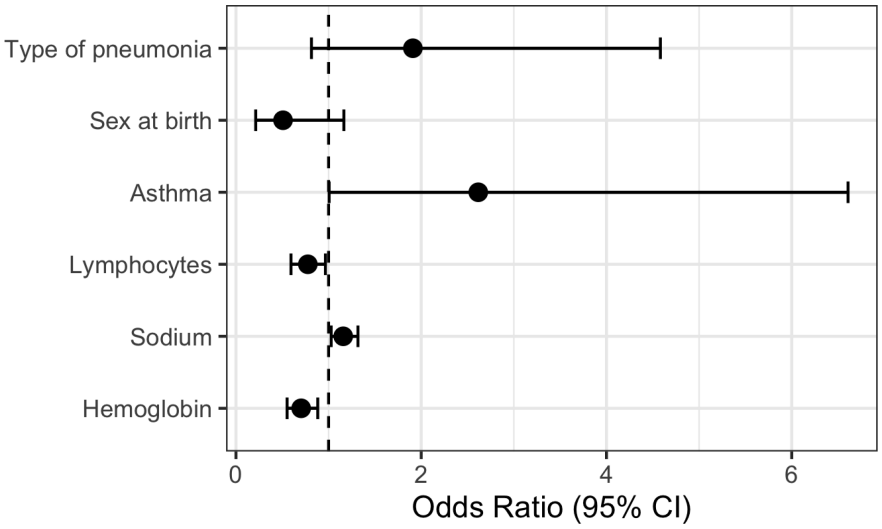

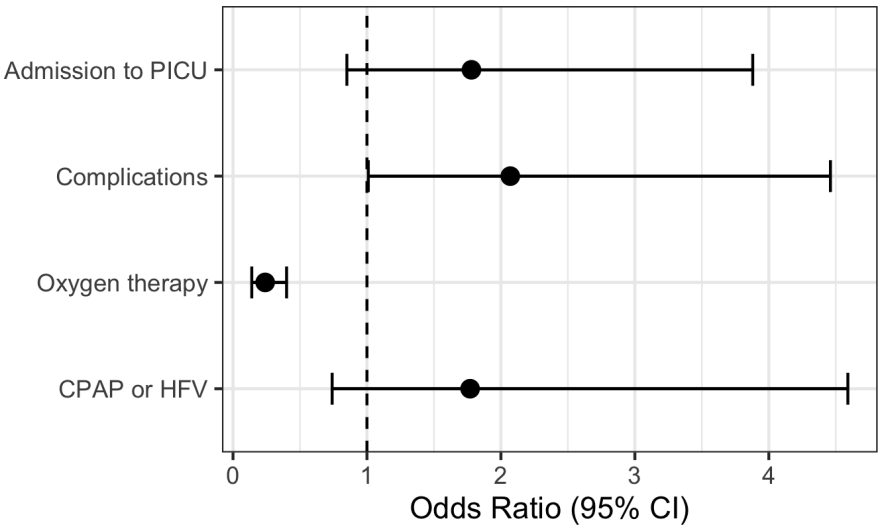

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