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Increased severity of respiratory syncytial virus airway infection due to passive smoke exposure

Clemens Maedel MD[1] | Katharina Kainz MD[1] | Thomas Frischer MD[1,2] | Matthias Reinweber MSc[3] | Angela Zacharasiewicz MD, MBA[1]

[1] Department of Pediatrics, Teaching Hospital of the University of Vienna, Wilhelminen Hospital, Vienna, Austria

[2] Faculty of Medicine (Medical School), Sigmund Freud University Vienna, Vienna, Austria

[3] Vienna Hospital Association, Clinical Research Center, Vienna, Austria

Correspondence
Angela Zacharasiewicz, MD, MBA, Department of Pediatrics, Wilhelminen Hospital, Montleartstrasse 37, 1160 Vienna, Austria.
Email: angela.zacharasiewicz@wienkav.at

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Abstract

Objective: Aim of this study was to analyze whether children with objectively measured second-hand cigarette smoke (SHS) exposure suffer from a more severe course of disease when hospitalized with lower respiratory tract infection (LRTI) due to respiratory syncytial virus (RSV).

Methods: This prospective study was conducted at the Department of Pediatrics, Wilhelminen-Hospital, Vienna, Austria in children aged below 1 year without a history of preceding lung disease and with acute symptoms of LRTI and a positive nasopharyngeal swab for RSV. On admission, urinary cotinine was measured as a marker of recent SHS and clinical severity of LRTI was assessed by oxygen saturation SpO_2 and the "admission clinical severity score" (CSSA). Parents/caregivers were asked to complete a customized questionnaire assessing risks for SHS and demographic characteristics.

Results: After inclusion of 217 patients, data of 185 patients with a mean (SD) age of 106 days (80) were analyzed. Twenty-five patients (13.5%) were "cotinine-positive" (COT+) defined as a urinary cotinine level of ≥7 µg/L. SpO_2 on admission was significantly lower in children recently exposed to SHS defined objectively by COT+ (94.8% ±2.0) in urine on admission compared to children not recently exposed (COT−) (96.8% ±3.0; $P < 0.01$). Disease severity, assessed via mean clinical severity score on admission (CSSA) for COT+ and COT− was 2.56 and 1.71, respectively ($P = 0.03$).

Conclusions: Recent exposure to SHS was associated with lower O_2 saturation and higher clinical severity score, measured by urine cotinine levels in children hospitalized for RSV infection under 1 year of age.

KEYWORDS
bronchiolitis, cotinine, lower respiratory tract infection, nicotine, RSV, second-hand smoke

Abbreviations: ANOVA, analysis of variance; CCR, cotinine-to-creatinine-ratio; COT+, cotinine-positive patient; COT−, cotinine-negative patient; CSSA, admission clinical severity score; ERS, European Respiratory Society; L, liter; LRTI, lower respiratory tract infection; MANOVA, multivariate analysis of variance; µg, microgram; mL, milliliter; O_2, oxygen; OGP, Osterreichische Gesellschaft Pneumologie - Austrian Society for Pulmonology; PCR, polymerase chain reaction; RSV, respiratory syncytial virus; SD, standard deviation; SHS, second-hand cigarette smoke; SpO_2, oxygen saturation in %.

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1 | INTRODUCTION

Second-hand cigarette smoke (SHS) is a prevalent and dominant indoor air pollutant that has major effects on the health of children. It is estimated, that 40-50% of children worldwide are regularly exposed to SHS, primarily by being around smoking parents and/or other household members.[1,2] Nicotine is distilled from burning tobacco, carried on tar droplets and inhaled both by active smokers, but also by children being around smokers.[3,4] Apart from this type of uptake, nicotine is also ingested as residual tobacco smoke pollutant remaining on surfaces and in dust via inhalation, ingestion, or dermal contact referred to as third hand smoke.[5]

Children living in homes with self-reported smokers have more severe respiratory illnesses than those living in homes with no smokers, and infants and children exposed to SHS have more cough, wheeze and mucous production.[6–9]

Recently, elevated hair nicotine values in infancy were found to be risk factor for wheezing and asthma in children.[10] Nicotine is extensively metabolized, primarily in the liver, and its major proximate metabolite is cotinine in plasma.[7,11] Urinary cotinine concentrations are on average four- to five-fold higher than in plasma, making urine a more sensitive medium for the detection of low-level exposure to tobacco smoke like SHS.[12] Liquid chromatography tandem mass spectography is the gold-standard in measuring the urinary cotinine levels.[13]

Human respiratory syncytial virus (RSV) is the most common cause of acute respiratory tract infection in infants,[14] occurring in 50% of children during the 1st year of life.[15] Severity of disease ranges from rhinitis to severe lower respiratory tract infection (LRTI), requiring intensive care treatment. LRTI caused by RSV infection leads to hospitalization in between 1% and 2.5% of all infants[16,17] and 66 000-199 000 deaths per year may be linked to RSV infection worldwide.[18] A recent study has shown that diagnostic and therapeutic measures for RSV LRTI vary widely between different countries and hospital sites.[19]

There is growing evidence that SHS exposure may increase disease severity of RSV-associated airway infections.[16,20–23] First, a higher rate of hospital admission for RSV-associated LRTI has been found in children who were reported to have been exposed to second-hand smoke.[9,21–23] Second, data published by Bradley et al[20] indicate that infants with RSV infection exposed to SHS at home, again assessed by a subjective method of self-report of caretakers, have a significantly lower oxygen-saturation (SpO_2) during hospitalization than those not exposed. Finally, Semple et al[16] showed that children, who had a reported history of exposure to SHS, more frequently need supplemental oxygen and mechanical ventilation.

Aim of this study was to analyze for the first time using objective markers of SHS exposure via urine cotinine levels on admission, whether children admitted to hospital due to RSV LRTI have lower oxygen saturation on admission and a more severe course of disease after being recently exposed to nicotine.

2 | MATERIALS AND METHODS

The study was conducted at the Department of Pediatrics, Wilhelminen Hospital Vienna. Inclusion criteria were clinical signs of LRTI, severe enough to require Emergency Department care or hospitalization. Our study protocol was set up for two RSV seasons, with a minimum amount of patients calculated by a power analysis based on the data of Bradley et al[20] concerning the O_2 saturation changes (RSV bronchiolitis and SHS vs RSV bronchiolitis without SHS). According to this, a sample size of 67 patients would have been needed to identify statistically significant differences between the groups (mu [0]: 92,2%; mu [1] 88,8%, Sigma: 7, Alpha: 0,05, Power 0,80, two sided test). The aim of the study was to assess a possible association of nicotine, as a marker for SHS, on severity of RSV infection, therefore a control group (eg, RSV negative) was not required.

Infants were screened and recruited consecutively at the Outpatient Clinic of the Department. Urine samples were obtained within the first 12 h of admission, in children aged 1 year or younger with symptoms of LRTI and a positive nasopharyngeal swab test for RSV (Alere BinaxNOW RSV Card, Alere Scarborough, Inc., Scarborough, ME). To confirm the sensitivity of the instant swab test, 52 patients (28.1%) were tested randomly by performance of a RSV polymerase chain reaction (PCR) which confirmed RSV presence in all 52 (100%) swab-positive patients being tested. Children with negative RSV swab tests were not included in the study.

Exclusion criteria were defined as follows: any pre-existing lung disease including recurrent wheezing episodes and chronic lung disease of prematurity/bronchopulmonary dysplasia.

All research and measurements followed the tenets of the Declaration of Helsinki, and the local ethics committee approved the study, all parents/caregivers gave their written informed consent in German language. Translation by professional interpreters was performed as needed.

After enrolment, oxygen saturation at rest was measured without supplemental oxygen (Pulse Oximeter Model PM-7000, ShenZhen Mindray Bio-Medical Electronics Co., Ltd., Hamburg, Germany or Model 515b, NovaMetrix Medical System, Inc., Wallingford, CT) and all other clinical parameters were recorded according to study protocol. With regards to measuring disease severity objectively, Bamberger et al[24] already described a score, which has been shown to be useful to grade disease severity in patients with RSV: the “admission clinical severity score” (CSSA) (Table 1). The CSSA score is a non-validated commonly used clinical scoring system designed for assessing the severity of RSV infection on admission into the hospital. Scoring was performed by the pediatrician in charge in the outpatient clinic. Decisions were made by one doctor only. All doctors were trained regarding study participation, including relevant in- and exclusion criteria, informed consent, physical examination, and for completion the clinical scores.

Parents/caregivers were asked to complete a customized questionnaire including information on demographic factors such as apartment size, number of siblings, family history of asthma or other lung diseases, and known risk factors for severe RSV infection such as

TABLE 1 Composition of the "clinical severity score at admission" (CSSA)

Scoring	0	1	2
Sign/symptom auscultated breath sounds/air exchange	Mild	Moderate	Severe
Respiratory rate	≤64 min	65-70 min	>70 min
Breathing behavior	None to mild intercostal retractions or nasal flare	Moderate intercostal retractions and suprasternal retractions. Grunt, flare	Severe intercostal retractions. Flaring, subcostal retractions
O_2 saturation	>92%	90-92%	<90%
Airway secretions	Rhinorrhea	Frequent cough, gag, increased secretions	Inability to clear secretions

Bamberger et al.[24]

prematurity and concomitant diseases, furthermore birth weight and age-adjusted weight and detailed information on parental smoking (Table 2). We defined the exposure level of reported second hand smoke (based on the questionnaire) as follows: (1) SHS 0: no reported exposure; (2) SHS 1: low-level exposure: at least one family member smoking at home, excluding the mother; and (3) SHS 2: high-level exposure: a smoking mother and/or smoking mother in pregnancy. The questionnaire was available in German, Croatian, and Turkish language.

A urine sample was collected, and cotinine was measured using chromatography tandem mass spectography. Using an API 4000 LC-MS/MS System (Sciex, Inc., Toronto, Canada) as described previously.[25] Standards and calibrators were obtained from Recipe (RECIPE Chemicals + Instruments GmbH, Munich, Germany). Urinary cotinine half-life has been reported to be 6-22 h,[26,27] which makes cotinine a reliable indicator for recent SHS exposure within a maximum of 1 day.

Urinary cotinine values were recorded as the objective marker for SHS and the lower limit of detection (7 µg/L) was used as a threshold. Values above detection limit were defined as positive samples (COT+) because the presence of cotinine in urine was proven. Urinary cotinine can only be a result of the child's exposure to nicotine, and irrespective of whether nicotine entered the body by inhalation or by direct resorption through the skin,[3,5] nicotine itself is the only source of cotinine in urine currently known. In order to investigate the dose-effect of cotinine on the primary endpoint SpO_2 and to compensate for potential dilution effects, urinary creatinine was determined on an automated clinical chemistry analyzer (Roche Cobas 8000, Roche Diagnostics, Risch-Rotkreuz, Switzerland), by an enzymatic test using a modified Jaffe reaction according to manufacturer's instructions. Subsequently, the cotinine-to-creatinine-ratio (CCR) was calculated.[28]

Data were collected in dedicated case report forms (CRFs) and analyzed using SPSS Statistics 24.0 for Windows and 21.0 for Mac (both IBM, Armonk, NY).

Descriptive data are shown as means ± SD and range. Distribution of data was checked with the Kolmogorov-Smirnov test. Not normally distributed data were analyzed with a univariate analysis (ANOVA), if not stated otherwise. Dichotomous outcomes were tested with the chi-square test, for multiple group comparisons a multivariate analysis of variance (MANOVA) was used. A linear regression model/logistic regression model was calculated to investigate the influence of demographic factors such as apartment size, sibling factors, prematurity, smoking during pregnancy, concomitant lung diseases, birthweight, and gestational age adjusted birth weight and age adjusted weight on admission on SpO_2 and on cotinine levels.

3 | RESULTS

During a period of two RSV seasons between 2015 and 2017, a total of 217 patients were enrolled, out of which 32 patients (14.7%) had to be excluded (Figure 1).

Hence, data of 185 children were included into the analyses. Mean (standard deviation [SD]) age of the study population was 106 days (±80) with a male: female ratio of 53%:47%. For 10 patients, questionnaire data on SHS were missing. First, concerning

TABLE 2 Composition of SHS groups 0-2

Group	Interpretation	Conditions		
SHS0	No SHS exposure	Smokers in same household? Maternal smoking during pregnancy?	No No	And
SHS1	Low SHS exposure	Smokers in same household? Who is smoking in same household?	Yes Father, siblings, others	And
SHS2	High SHS exposure	Maternal smoking during pregnancy? Smokers in the same household? Who is smoking in same household?	Yes Yes Mother	Or And

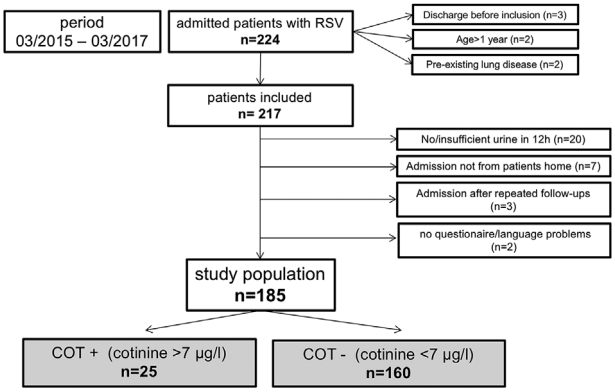

FIGURE 1 Flowchart of patient recruiting and reasons for exclusion

possible confounders, a linear regression model was calculated, which could show that neither apartment size ($P > 0.54$) nor birthweight ($P > 0.35$), preexisting allergies ($P > 0.89$), familial lung diseases ($P > 0.87$) or asthma in the family history ($P > 0.32$), gestational age-adjusted birthweight ($P > 0.63$), gestational age/prematurity ($P > 0.50$), age-corrected weight at admission ($P > 0.62$), number of siblings ($P > 0.26$), or smoking during pregnancy ($P > 0.347$) are a predictor for SpO_2 values. Second, a logistic regression model was calculated, which could show that neither apartment size ($P > 0.28$) nor birthweight ($P > 0.73$), preexisting allergies ($P > 0.15$), familial lung diseases ($P > 0.72$), asthma in the family history ($P > 0.22$), gestational-adjusted birthweight ($P > 0.88$), gestational age/prematurity ($P > 0.57$), age-corrected weight at admission ($P > 0.48$), or number of siblings ($P > 0.95$) are predictors for cotinine. Smoking during pregnancy could be identified as a predictor for cotinine ($P > 0.01$).

Cotinine could be identified as the only predictor for SpO_2 in this model ($P < 0.001$).

Twenty-five (13.5%) patients were found to be "cotinine positive" (COT+) defined as a urinary cotinine level of ≥7 µg/L on admission. COT+ patients had significantly lower birthweight (3186.9 g; ±517.2) than COT− patients (3456.2 g; ±589.2; $P < 0.05$). Demographic characteristics for "cotinine positive" (COT+) and "cotinine negative" (COT−) patients were similar (Table 3).

Mean (SD) SpO_2 on admission for COT+ and COT− children was 94.8% (±2.0) and 96.8% (±3.0), respectively ($P < 0.001$) (Figure 2).

Mean CSSA score for COT+ and COT− patients was 2.56 (±2.22) versus 1.71 (±1.71), respectively ($P < 0.05$) (Figure 3).

Most patients needing supplemental oxygen on admission (defined as patients with a SpO_2 <92%) were actually found within the COT+ patient group (28% for COT+ compared to 4% for COT−; $c^2_{(3175)} = 19.25$, $P < 0.01$).

As defined prior to study start, all children were divided into exposure groups according to the reported SHS exposure assessed by questionnaire. Hence, a total of 175 patients were divided into three groups according to their SHS exposure status: no reported exposure "no SHS" (group 0; $n = 82$), "low level SHS" (group 1; $n = 41$), and "high level SHS" (group 2; $n = 27$) (Table 2). With regards to a potential correlation between cotinine status and the questionnaire response concerning smoking—described using the allocated SHS group—there were statistically significantly more COT + patients in the high-level SHS group 2 ($c^2_{(3175)} = 26.57$, $P < 0.001$). However, in the group of patients without a reported history of SHS exposure (SHS 0 group), 3 (12%) infants were found to actually be COT+ patients.

There was no difference in SpO_2 on admission between the three groups of self-reported SHS ($P = 0.47$). No relation between SHS groups and CSSA scores ($P > 0.1$) was observed either. In order to establish what the effect was of *actual recent nicotine exposure* with proven cotinine in urine as compared to *reported, but without measured exposure* on admission was and to hence better distinguish reported (questionnaire) from recent exposure (COT+) effects all COT+ patients were separated from and compared to these three

TABLE 3 Demographics of COT+ and COT− patients (Mean [SD; range])

	COT+	COT−	
n	**25**	**160**	***P*-value**
m:f (%:%)	44%:56%	55%:45%	0.295
Age (days)	120.4 (±88.7)	107.1 (±74.7)	0.441
Age-adjusted weight on admission (g)	6401.2 (±1649.5)	6021.6 (±1688.4)	0.296
Prematurity (GA <37 + 0)%	10.80%	0.50%	0.317
Week of gestation (in weeks)	39 (±1.5)	39 (±1.8)	0.727
Birthweight (g)	3186.9 (±517.2)	3456.3 (±589.2)	0.032
Preexisting allergies (%)	0%	1.3%	0.575
Family history: asthma (%)	24%	13.80%	0.188
Family history: lung diseases (%)	12%	8.80%	0.608
Apartment size (m^2)	67.5 (±42.6; 34-260)	73.2 (±35; 20-240)	0.476

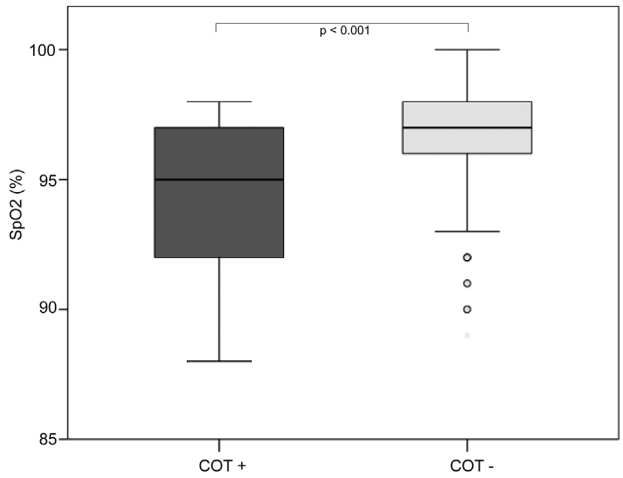

FIGURE 2 Boxplot: SpO_2 (%) on admission for COT−(left box) and COT+ (right box)

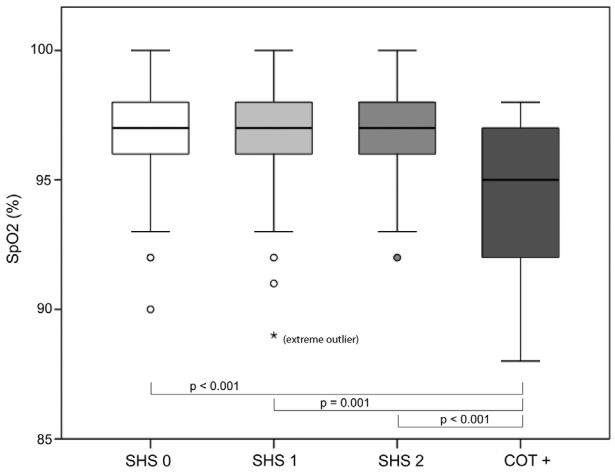

FIGURE 4 Boxplot: SpO_2 (%) on admission for SHS0, SHS1, SHS2, and COT+

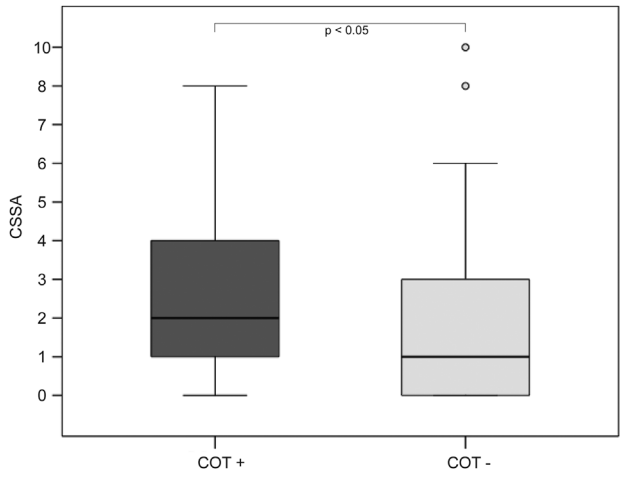

FIGURE 3 CSSA for COT−(left box) and COT+ (right box)

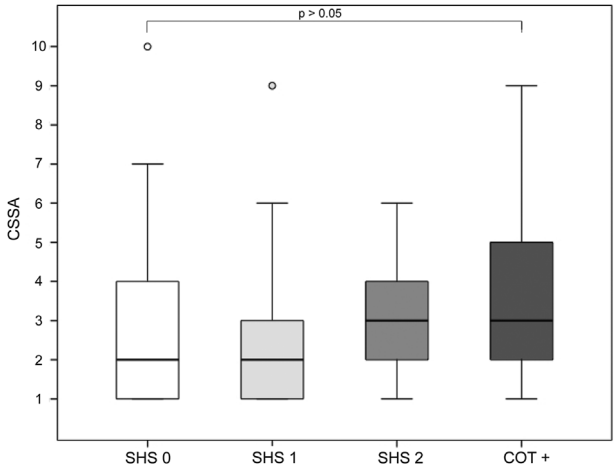

FIGURE 5 Boxplot: CSSA for SHS0, SHS1, SHS2, and COT+ (concerning boxplots: circles indicating outliers, asterisks are indicating extreme outliers)

SHS groups. Within this comparison, the groups significantly differed in SpO_2 ($P < 0.001$). SpO_2 was lowest for COT+ patients compared to all three COT− exposition groups (Figure 4). No significant differences in CSSA was found ($P < 0.08$) between these four groups (Figure 5). However, when a contrast analysis was performed, a significant effect was detected for a linear correlation. It shows a linear increase of CSSA across all groups with its highest in the COT+ group ($P < 0.05$).

No correlation between the level of cotinine corrected for dilution, using the CCR, and SpO_2 ($P > 0{,}66$), and CCR and CSSA ($P > 0{,}659$) were found.

4 | DISCUSSION

To our knowledge, this study has shown for the first time that in children hospitalized with RSV infection, SHS exposure assessed objectively is associated with lower oxygen saturation on admission and a worse overall clinical score. SHS exposure was measured using objective cotinine measurements, which is the major metabolite of tobacco smoke's main pollutant nicotine. There are various studies which have shown that subjectively detected SHS exposure has a negative impact on the clinical outcome in RSV bronchiolitis[1,23] and other respiratory diseases[29] but to our knowledge, there is no such evidence in combination with the objective measurement of nicotine smoke exposure in children. Questionnaire data on smoking behavior are at risk of reporting bias,[30] as patients'/caregivers' compliance and willingness to answer questions may vary. In our study, a small number of parents/caregivers was found who had denied SHS exposure, but whose children nevertheless had elevated urinary cotinine levels implying underreporting of exposure. Therefore, urinary cotinine can be used as an objective indicator for SHS.[30]

Furthermore, we have shown for the first time that children with objectively verified recent nicotine exposure had significantly lower SpO_2 values than children without recent exposure. These COT+ children had even lower SpO_2 than children, who had subjectively reported SHS in general, irrespective of the amount of reported SHS by questionnaire, but who were not recently exposed.

The analysis provides statistically significant higher CSSA scores in COT+ patients compared to COT− patients. In addition, there was a linear trend for higher CSSA scores across the groups with positive reported SHS as well as the exposure-verified COT+ patient group. Higher self-reported SHS exposure resulted in higher CSSA scores, with their maximum for COT+ patients compared to the SHS groups.

Moreover, in our study population, COT+ patients were statistically significantly more frequently in need of supplemental oxygen therapy on admission (SpO_2 <92%) compared to those with only parents' report of past SHS exposure. Our Department's policy as part of a communal hospital is to admit children with RSV LRTI irrespective of oxygen saturation on admission.

In our study, a cut-off value for COT+ patients of ≥7 μg/L was used; this definition reflects the detection threshold of the measurement technique. Other studies have reported slightly lower cut-off values[23–26] and if lower cut-off values had been used, we might have found more children with low-level proven nicotine exposure; however, we were limited by our measurement method.

According to the analysis of the questionnaire used in this study, 40% of infants are exposed at a regular basis to tobacco smoke in their homes. One possible explanation why the number of cotinine containing urine samples was considerably lower than the number of the nicotine-exposed infants according to the reported high prevalence of exposure could be the time delay in urine sampling due to waiting times after arrival to the outpatient clinic. Additionally, we defined a maximum time span of 12 h for urine sampling in the study protocol, which may have been enough time for urinary cotinine to be eliminated and fall under the detection threshold. Another possible explanation may be that parents and other household members actually stop smoking around an obviously ill child with respiratory symptoms such as coughing and wheezing. In this case, children may not be detected as "recently exposed" to SHS, but under normal circumstances, when not acutely ill, they are routinely exposed to SHS in their daily life.

Another reason for questionnaire reported high-level SHS exposure and at the same time measured COT-negativity in the urine sample may be "diluting effect" of smoking in large apartments or smoking in designated rooms in absence of children, resulting in negative COT measurements in urine.

Beside this, in our study population, COT+ patients had statistically significant lower birthweight than COT− patients; however, birthweight had no measurable effect on the relationship between the primary endpoint SpO_2 and cotinine exposure. This might be an effect of smoking in pregnancy, because heavily smoking mothers are likely to also smoke during pregnancy and this has been shown to have an effect on birth weight.[31]

One limitation of our study was that our questionnaire did not include the question of recent SHS within the last 24 h. It might be recommendable to add a question about recent SHS exposure in future questionnaires; however, when designing our questionnaire, we felt that asking about actual recent tobacco exposure in children with current respiratory illness was too suggestive.

Various potential sources of confounding need to be considered, when discussing severity of RSV bronchiolitis. We have excluded all children with any pre-existing lung disease including recurrent wheezing episodes and chronic lung disease of prematurity/bronchopulmonary dysplasia as these are known risk factors for severe RSV infection. Children with clinically severe RSV bronchiolitis needing intensive care treatment were also not included into our study, because these children were transferred to intensive care unit directly. Based on our exclusion policy, in our model prematurity, low birth weight (gestational age controlled), age adjusted weight on admission, as main risk factors for a more severe course of RSV bronchiolitis were not found to be a risk factor for worse outcome in our study population; in our model only urinary cotinine levels were found to be associated with our primary outcome parameter SpO_2.

Smoking is more prevalent in lower socioeconomic classes where poverty is more prevalent and this could introduce a bias. More affluent parents might be more likely to be presenting to the hospital as they are less constrained by cost. However, this is unlikely to be the case in the reported study population—in Austria presentation to the hospital is free of charge for children, as well as transportation to the hospital when calling the ambulance. Therefore lower socioeconomic class is unlikely to be a major source of bias in this specific healthcare setting in Austria.

We found an association of urinary cotinine and more severe RSV infection; nevertheless, this does not necessarily prove causation. We measured cotinine as the major metabolite of nicotine and due to the numerous publications on the detrimental effects of nicotine on children's health,[6,8,29] nicotine is our main suspect. The association found may theoretically also be caused by another factor associated with tobacco smoking, for example another product related to smoking, which may actually be the reason for a more severe disease course.

However, an association of recent nicotine exposure with disease severity has been shown, this makes electronic cigarettes and other forms of nicotine replacement unlikely to be healthy and safe. Future research is needed to confirm this association.

The long-term effects of passive smoke exposure on patients' overall and respiratory health have been shown in various clinical trials.[1,6,7,16,20,22,23,29] This study followed infants during the acute stage of the RSV LRTI disease and during their hospital stay. An association for an immediate effect on the clinical state was demonstrated.

5 | CONCLUSION

This study found an association between children with RSV LRTI and recent, objectively measured SHS exposure (measured by urinary cotinine levels) and lower oxygen saturation as well as a worse clinical

condition than in children without recent SHS exposure. Future research is needed to confirm this association.

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CONFLICTS OF INTEREST

All authors have indicated they have no potential conflicts of interest and no financial relationships relevant to this article to disclose.

AUTHORS' CONTRIBUTION

Drs CM, TF, and Dr AZ conceptualized and designed the study, drafted the initial manuscript, and reviewed and revised the manuscript. Drs CM and KK designed the data collection instruments and collected data. Dr CM carried out the analyses and coordinated and supervised data collection. MR, performed advanced statistical analyses. All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work. Preliminary results were presented at the OGP 2016 congress in Vienna and the ERS 2017 congress in Milano.

ORCID

Clemens Maedel http://orcid.org/0000-0003-1830-5833
Angela Zacharasiewicz http://orcid.org/0000-0002-0511-2138

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