The clinical and chest radiographic features of respiratory syncytial virus-associated severe respiratory illness in hospitalised adults in South Africa, 2022 - 2023

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Background. In most healthy adults, respiratory syncytial virus (RSV) causes mild self-limiting respiratory infection. However, vulnerable populations may present differently or have more complicated courses of disease.

Objectives. To describe the clinical and radiographic features of adults hospitalised with RSV-associated severe respiratory illness (SRI) in two urban hospitals during 2022 and 2023.

Methods. Patients aged ≥18 years were enrolled through systematic sentinel surveillance for SRI. Clinical characteristics and radiographic profiles of RSV-infected adults were reviewed.

Results. Eighteen (2%) of 916 enrolled hospitalised patients with SRI tested positive for RSV at the two hospitals. Other pathogens detected included SARS-CoV-2 (*n*=69/916; 8%), influenza (*n*=49/916; 5%) and pertussis (*n*=10/916; 1%). The median (range) age was 50 (35 - 75) years, and 12 (67%) were female. All had at least one comorbidity, including immunocompromising conditions (*n*=15/18; 83%), metabolic conditions (*n*=8/18; 44%), structural lung disease (*n*=12/18; 66%) and cardiovascular conditions (*n*=3/18; 16%). Among persons living with HIV (*n*=11/18; 61%), 72% (*n*=8/11) had suppressed HIV viral loads, and 9/11 (81%) had CD4 counts <250 cells/μL. Median (range) length of hospital stay was 4.5 (1 - 15) days. All patients received empirical antibiotics, intravenously in 12/18 (66%); only 5/12 (41%) de-escalated to oral antibiotics. Radiographic findings demonstrated post-tuberculosis lung disease (PTLD) in 50% of patients (*n*=9/18), of whom 11 (61%) had new ground-glass opacifications, with lobar v. diffuse in 55% (*n*=6/11) v. 45% (*n*=5/11).

Conclusion. The high prevalence of underlying conditions in adults with RSV-associated SRI, specifically HIV and PTLD, suggests that targeted vaccination in these groups may prevent hospitalisation with RSV-associated SRI.

Keywords. Respiratory syncytial virus, RSV, viral pneumonia, severe pneumonia, severe respiratory illness, SRI.

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Study synopsis

What the study adds. This study identified a distinct clinical and radiographic profile of adults hospitalised with respiratory syncytial virus (RSV)-associated severe respiratory illness in South Africa, where HIV infection, post-tuberculosis lung disease (PTLD) and polysubstance-induced lung damage were the predominant comorbidities, unlike traditional cardiometabolic risk profiles seen elsewhere. It also found characteristic chest radiographic features such as lobar and diffuse ground-glass opacifications in these patients.

Implications of the findings. The findings suggest the need to expand RSV vaccination recommendation protocols to include younger adults with HIV and PTLD. They also highlight the importance of improving antimicrobial stewardship and developing better diagnostic tools to differentiate viral from bacterial infections. These findings are crucial in our high burden of disease setting.

Respiratory syncytial virus (RSV), from the family of *Paromyxoviridae*, is a respiratory virus with a highly contagious droplet mode of transmission, and typically causes self-limited mild respiratory infections.[1] RSV is well documented to be a cause of morbidity and significant mortality in paediatric populations, and causes complicated hospital stays in vulnerable adult population groups.[2] The spectrum of RSV disease severity varies in adults depending on age and comorbidities.[2,3] After inhalation, RSV causes bronchial epithelial cell damage and invokes a cytokine and chemokine response with resultant airway inflammation; the representation of this on a chest radiograph (CXR), especially in adults, is unclear.[4]

Vulnerable populations may have a longer length of hospital stay and possibly recurrent admissions.[3] RSV is not typically considered or tested for in emergency departments as a cause for patients presenting with clinical exacerbations of chronic lung or cardiovascular disease, especially in low-resourced settings.[5] The epidemiology of RSV in adults is currently under surveillance, and circulation declined during the COVID-19 pandemic, possibly owing to general measures employed for protection against COVID-19.[6] RSV seasonality and circulation have since returned to normal, but a change in seasonal patterns after the pandemic has been described.[6]

RSV is common in adults and can present more severely in elderly and immunocompromised patients, such as persons living with HIV (PLWH),[3,7] among whom increased RSV-associated hospitalisations and in-hospital mortality have been described.[7,8] However, these studies were conducted before the widespread availability of antiretroviral therapy and included limited clinical details. It is unclear to what extent the susceptibility of PLWH infected with RSV is reduced once immune reconstitution occurs.[8] It is also unclear to what extent underlying tuberculosis (TB) is a risk factor for severe RSV.[8,9]

This study aimed to describe the clinical features, radiographic profiles and outcomes of adult patients admitted to hospital with RSV-associated severe respiratory illness (SRI) at two hospitals in Cape Town, South Africa (SA).

Methods

Study design, population and setting

This was a descriptive study of all adults with laboratory-confirmed RSV requiring hospital admission at two urban academic hospitals in Cape Town over the 2-year period 3 January 2022 - 31 December 2023. Tygerberg Hospital is a tertiary academic hospital in Cape Town's Tygerberg Eastern Health District and is the largest hospital in the province, operating a total of 1 380 beds. Mitchells Plain Hospital is an academic district hospital in the Mitchells Plain subdistrict in the Cape metropolitan area and has a 395-bed capacity. Both hospitals serve large urban drainage areas with a high HIV and TB burden of disease. This is a descriptive substudy of the larger and ongoing National Pneumonia Surveillance Programme, conducted by the National Institute for Communicable Diseases (Stellenbosch University Health Research Ethics Committee (HREC) ref. no. S23/05/110). All adult patients aged ≥18 years who met the surveillance case definition for SRI and were enrolled after providing informed consent were included for analysis. SRI was defined as any patient requiring hospitalisation for either physician-diagnosed lower respiratory tract infection or suspected COVID-19 (of any symptom duration).

Laboratory methods and testing

A nasopharyngeal swab was collected from all patients who met the SRI case definition and were enrolled in the study. All samples were tested for RSV, influenza and SARS-CoV-2 using the Allplex SARS-CoV-2/FluA/FluB/RSV multiplex real-time polymerase chain reaction (PCR) assay (Seegene, South Korea). CXRs were performed as part of routine clinical care for patients with SRI.

Data collection

Demographic, clinical, treatment and outcome data for patients testing positive for RSV were retrieved from electronic medical records from the Enterprise Content Management (ECM) systems at the study hospitals. CXRs of confirmed PCR-positive patients were reviewed by a pulmonologist and a physician on the Picture Archiving and Communication System (PACS). The vaccination history for COVID-19 and influenza was retrieved using ECM and Single Patient Viewer (SPV).

The CXRs were compared with radiographs on previous admissions to define new radiographic findings. The length of stay of these patients and management outcomes were retrieved by reviewing the Electronic Continuity of Care Record (eCCR) and corroborated with an online booking system, CLINICOM. Comorbidities were classified as immunocompromising (HIV, active TB co-infection or diabetes mellitus), metabolic (hypertension, obesity or dyslipidaemia), structural lung disease (post-TB lung disease (PTLD), polysubstance use (smoking mandrax/methaqualone and/or cannabis), asthma or chronic obstructive pulmonary disease (COPD)), and cardiovascular (ischaemic heart disease or cardiomyopathy of any cause). Multimorbidity was defined as the presence of two or more comorbidities in the same patient. Baseline blood tests (white cell count (WCC), C-reactive protein (CRP), urea, creatinine, CD4 cell counts and HIV viral loads) were done at the discretion of the treating clinicians, and results were obtained from the National Health Laboratory Service Trakcare results system. By reviewing the medication prescribed by the primary physician, this study also identified whether antibiotics were given during the hospital stay and which antibiotics were administered. We captured the duration of antibiotics given and whether intravenous (IV) medications were de-escalated to oral formulations. Grading of the severity of illness was based on the level of care recorded during the patients' stay as well as additional examination findings such as hypoxia, measured as baseline room air oxygen saturation <90% (on pulse oximetry or arterial blood gas), and respiratory rate, where mild was defined as ≥24 and <30 breaths per minute (breaths/min), moderate distress as ≥30 and <35 breaths/min, severe as ≥35 and <40 breaths/min, and critical as ≥40 breaths/min.

Statistical analysis

We summarised continuous variables using means and standard deviations (SDs) for parametric data or medians and ranges for non-parametric data. Categorical variables were described using frequencies and percentages. Stata 18 (StataCorp, USA) was used for data analysis.

Ethical approval

Ethical approval for the substudy was obtained from the Stellenbosch University HREC (ref. no. S23/05/110 Sub Study N21/10/122).

Results

Clinical profiles

Over the 2-year study period, 18 (2%) of 916 enrolled hospitalised patients with severe respiratory illness tested positive for RSV in the two hospitals. Other pathogens detected included SARS-CoV-2 in 69/916 patients (8%), influenza in 49/916 (5%), and pertussis in 10/916 (1%). RSV subtype B, present in 13/18 (72%), was the predominant RSV subtype.

The median (range) age was 50 (35 - 75) years. Most patients were aged <60 years (*n*=12/18; 67%) (Tables 1 and 2), and most were female (*n*=12/18; 67%). The predominant documented presenting symptom was dyspnoea (*n*=17/18; 94%), with only one patient presenting with a cough as a predominant symptom. Vaccination history for COVID-19 and influenza was not well documented and was only recorded for 9/18 patients (50%). Six patients (*n*=6/9; 66%) were unvaccinated for COVID-19, and no patient had documented influenza vaccinations recorded.

Eleven patients (*n*=11/18; 61%) were hypoxic and 9/18 (53%) were tachycardic. On auscultation, diffuse crackles were a predominant finding in 13/18 patients (72%). Further, on examination, 11/18 patients (61%) had moderate respiratory distress, 2/18 (11%) had severe respiratory distress, and 3/18 (17%) were critical with findings of severe hypoxia and a respiratory rate ≥40 breaths/min (Table 2).

Co-infections, underlying comorbidities and multimorbidity

We noted that 2/18 patients (11%) were co-infected with influenza A (Table 1). All patients had tested negative for SARS-CoV-2. Two patients (*n*=2/18; 11%) also had confirmed pulmonary TB with a positive GeneXpert MTB/RIF (Cepheid South Africa, SA), diagnosed on the current hospital admission. Cryptococcal meningitis co-infection, managed appropriately, was present in one PLWH (*n*=1/18; 5%), who had an elevated HIV viral load.

All patients had one or more comorbidities, including immunocompromising conditions (*n*=15/18; 83%), metabolic conditions (*n*=8/18; 44%), structural lung disease (*n*=12/18; 66%) and cardiovascular conditions (*n*=3/18; 16%) (Table 3). Multimorbidity was present in 89% (*n*=16/18). Among PLWH (*n*=11/18; 61%), 72% (*n*=8/11) had suppressed HIV viral loads, and most (*n*=9/11; 81%) had CD4 counts <250 cells/μL. Most PLWH were female (*n*=9/11; 82%). Diabetes was present in 3/18 (17%) and hypertension in 6/18 (33%), of whom 2/6 (33%) were also documented to have obesity and 2/6 (33%) were dyslipidaemic. Three of the 18 patients (16%) were documented to have clinical evidence of a cardiomyopathy.

Underlying structural lung disease was present in 12/18 (67%) of the patients, of whom 9/18 (50%) had PTLD, with 6/9 (66%) having radiographically significant features of PTLD. Eight (*n*=8/18; 44%) had underlying COPD, and 7/18 (39%) had superimposed structural changes due to inhaled polysubstance use. Two patients (2/18; 11%) had asthma. Eight patients (8/18; 44%) had normal background lung architecture on CXR imaging (Tables 1 and 3).

Radiographic analysis

Most patients had similar characteristic CXR features (Table 1), with 11/18 (61%) having ground-glass opacifications, 6/11 (54%) having a lobar ground-glass pattern, and 5/11 (45%) having a diffuse ground-glass pattern (Fig. 1).

We further noted that 5/18 patients (28%) had new nodular infiltrates on this admission that were not present on CXRs from previous admissions (Fig. 2). Only one patient (1/18; 5%) was noted to have a dense lobar consolidation; this patient was also managed for a community-acquired bacterial pneumonia.

Laboratory results

The median (range) WCC was 14.5 (4.6 - 31) × 10^9L and the median CRP, measured in 8/18 patients, was 66 (43 - 332) mg/L (Table 4). These levels were elevated in most of the patients, with the WCC elevated in 59% (*n*=10/17) and CRP in 63% (*n*=5/8). Biochemical measurements revealed a median (range) urea level of 8.08 (3.3 - 32.9) mmol/L and a mean (SD) creatinine level of 159 (43) μmol/L.

Management and outcome

All 18 patients received at least one antibiotic during their admission. Most patients (*n*=12/18; 66%) received IV antibiotics, of which ceftriaxone was the most commonly prescribed (*n*=11/12; 91%). Azithromycin was co-prescribed in 5/12 of the patients (41%) in addition to an IV antibiotic. Oral amoxicillin-clavulanic acid was prescribed in 6/18 patients (33%), with amphotericin B and flucytosine prescribed in one patient who had cryptococcal meningitis. Where data were available, only 5/12 patients (41%) who received IV antibiotics were de-escalated to oral antibiotics. The median (range) length of stay was 4.5 (1 - 15) days, and the median duration of antibiotics was 4 (1 - 5) days. In-hospital mortality was 17% (*n*=3/18) and the 3-month survival rate was 83% (*n*=15/18). At 3 months, 6/18 patients (33%) had been readmitted for respiratory complaints, although these patients were not retested for RSV upon readmission.

Discussion

In this study, we found a high proportion of patients with multimorbidity, including underlying HIV and PTLD, among adult patients admitted to hospital with laboratory-confirmed RSV-associated SRI. We also found that all patients were prescribed a broad-spectrum antibiotic, mostly intravenously, throughout their hospital admission. Most of the patients also appeared to have characteristic CXR features, with lobar or diffuse ground-glass opacities, or diffuse nodular infiltrates. A large proportion of patients had CXR features of underlying PTLD.

The most common comorbidities in individuals with RSV-associated SRI were HIV and structural lung disease, specifically PTLD. While a high prevalence of HIV, including patients with suppressed HIV viral loads, was previously documented in an SA study by Moyes *et al.*[3] exploring the features of admitted patients with RSV, a link between PTLD and RSV does not appear to have been described before and will need to be explored in larger data sets. Patients with structural lung disease are likely to present with more severe symptomatic disease or respiratory distress owing to baseline impaired lung function and therefore compromised respiratory reserve, which may account for the need for hospitalisation.[10] A link between influenza and progression of TB has been described,[11] and further research is required to explore similar links between RSV and PTLD or active TB infection. Our findings also differ from studies in other settings where cardiometabolic comorbidities were more frequent, and patients in our study were also younger than described

Table 1. Baseline demographic, comorbidities and radiographic data among 18 adults aged ≥18 years with respiratory syncytial virus-associated severe respiratory illness, South Africa, 2022 - 2023

		Medical conditions					Co-infections		
Age (years)	Sex	HIV	Met	PSU	COPD	PTLD	OI	Influenza A	Chest radiographic features
35	F	+	-	-	-	-	-	-	Diffuse interstitial non-confluent nodular pattern, left more than right
44	F	+	-	-	-	-	CCM	-	Diffuse nodular infiltrates with bilateral ground-glass opacification
46	M	-	-	+	+	+	-	-	Bullous change right upper zone and ground-glass opacification left lower zone
65	M	-	+	-	-	-	-	-	Ground-glass opacification left lower zone
63	F	+	-	-	-	+	-	-	Diffuse nodular infiltrates and ground-glass opacification left lower zone
38	F	+	-	+	-	-	PTB	-	Diffuse background ground-glass opacification with bilateral lower-zone predominance
48	M	-	-	+	+	+	PTB	-	Large cavity right upper zone, pleural thickening and diffuse nodular infiltrates
40	F	+	-	+	+	+	-	-	Large left pulmonary artery. Bilateral upper zone nodules
49	M	+	-	+	-	+	-	+	Diffuse ground-glass opacification with background nodular infiltrates
51	F	+	+	-	-	+	-	+	New diffuse ground-glass infiltrates
64	F	-	+	-	-	-	-	-	Background of bilateral nodular infiltrates, more pronounced in right lower zone
54	M	+	+	+	+	+	-	-	Pleural thickening and diffuse micronodular infiltrates with involvement right more than left
50	M	-	-	-	+	-	-	-	Minimal ground-glass opacification in left lower zone
66	F	-	+	-	-	-	-	-	Minimal ground-glass opacification over right lung
40	F	+	-	-	-	-	-	-	Diffuse background ground-glass opacification with bilateral lower-zone predominance
41	F	+	-	+	+	-	-	-	Dense consolidation right upper zone more than right lower zone
75	F	-	-	-	+	+	-	-	Left mid-zone ground-glass opacification
69	F	+	-	-	+	+	-	-	Diffuse background structural lung disease and left pneumothorax

F = female; M = male; + = present; - = absent; Met = metabolic; PSU = polysubstance user; COPD = chronic obstructive pulmonary disease; PTLD = post-tuberculosis lung disease; OI = opportunistic infection; CCM = cryptococcal meningitis; PTB = pulmonary tuberculosis.

elsewhere, such as in a recent systematic review done in the USA.[12] The differences in cardiometabolic comorbidities in our study may be related to the lower life expectancy in SA[13] or the higher burden of HIV and TB-related lung disease in the younger population.[14,15] With the growing surge of polysubstance use, including mandrax and cannabis, in Cape Town, polysubstance-induced chronic lung changes also create a vulnerable population group.[16]

Current Centers for Disease Control (CDC) guidance for RSV vaccination in adults recommends vaccination of adults aged ≥75 years or those aged between 60 and 74 who are at risk of severe disease.[17] These risk factors include traditional cardiometabolic risk factors such as chronic cardiovascular diseases, chronic lung diseases (COPD, asthma and interstitial lung disease) and end-stage renal disease, among others.[17] Three RSV vaccines are currently available for adults aged ≥60 years, GSK's Arexvy, Moderna's mResvia and Pfizer's Abrysvo, but licensed indications do not include risk factors detected in our study setting, which suggests that younger patients, specifically those with HIV and TB-related lung disease, may benefit from vaccination.[17,18]

In contrast to what is described internationally,[19] we found a female predominance in the present study, mirroring an earlier larger SA cohort[7] where a female predominance was noted to be statistically significant. In the same earlier study, a large proportion of these female patients were also HIV infected. The proportion of females with HIV in our study was also higher than that of males, in keeping with background HIV rates in female adults,[20] which probably contributes to the higher RSV hospitalisation rates seen in females.

This study also highlighted the nonspecific nature and varying clinical presentations of RSV-associated SRI. Most of our patients also had elevated markers of inflammation, specifically WCC and CRP, which adds to the difficulty in distinguishing severe RSV-associated SRI from bacterial pneumonia or superimposed bacterial infections

Table 2. Clinical features at presentation among 18 adults aged ≥18 years with respiratory syncytial virus-associated severe respiratory illness, South Africa, 2022 - 2023

Variable	*n* (%)
Age (years)	
35 - 39	2 (11)
40 - 49	7 (39)
50 - 59	3 (17)
60 - 69	5 (28)
70 - 75	1 (5)
Symptoms at baseline	
Dyspnoea	17 (94)
Cough	1 (6)
Clinical findings at baseline*	
Fever	1 (6)
Tachycardia	9 (53)
Hypoxia	11 (61)
Auscultation findings	
Crackles	13 (72)
Bronchial breathing	2 (11)
Wheezes	2 (11)
Normal lung sounds	1 (5)
Clinical severity†	
Mild	2 (11)
Moderate	11 (61)
Severe	2 (11)
Critical	3 (17)

bpm = beats per minute; breaths/min = breaths per minute.
*Fever was defined as a temperature >37.5°C, tachycardia as a documented heart rate >100 bpm, and hypoxia as oxygen saturation on room air <90%. Some patients were noted at baseline evaluation to have more than one clinical finding in the respective areas reviewed.
†Clinical severity was defined as respiratory rate findings where mild was ≥24 and <30 breaths/min, moderate distress was ≥30 and <35 breaths/min, severe was ≥35 and <40 breaths/min, and critical was ≥40 breaths/min.†

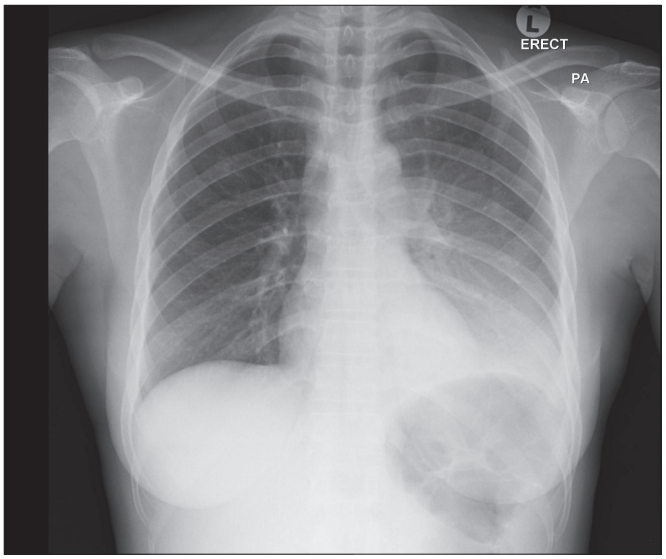

Fig. 1. Lobar ground-glass opacification in a patient with respiratory syncytial virus-associated severe respiratory illness with no other co-infections on this presentation.

Table 3. Comorbidities among 18 adults aged ≥18 years with respiratory syncytial virus-associated severe respiratory illness, South Africa, 2022 - 2023

Comorbidities	*n* (%)
Immunocompromised	
HIV infected	11 (61)
Active TB co-infection	2 (11)
Diabetes mellitus	3 (17)
Metabolic comorbidities	
Hypertension	6 (33)
Obesity	3 (17)
Dyslipidaemia	3 (17)
Structural lung disease	
PTLD	9 (50)
Polysubstance use (mandrax and cannabis)	7 (39)
Asthma	2 (11)
COPD	8 (44)
Cardiovascular disease	
Ischaemic heart disease	1 (5)
Cardiomyopathy	3 (17)
Multimorbidity	
1 comorbidity	2 (11)
2 comorbidities	7 (39)
3 comorbidities	4 (22)
4 comorbidities	2 (11)
5 comorbidities	3 (17)

TB = tuberculosis; PTLD = post-TB lung disease; COPD = chronic obstructive pulmonary disease.

on clinical findings or basic laboratory findings alone.[21] We also noted that two patients were co-infected with RSV and influenza. PLWH have an altered microbiome and may be co-infected with other pathogens at various stages of HIV; however, the underlying mechanisms are complex, and larger studies are required to investigate this further.[22] The study also highlights the challenge of optimising antimicrobial stewardship, and better diagnostic point-of-care tests for rapid identification of respiratory viral and/or bacterial infection are required to avoid antibiotic misuse.

Despite the high burden of RSV, radiographic features, especially in adults, are not well described in an SA setting. We describe distinct CXR features, specifically lobar and diffuse nodular infiltrates, as well as lobar ground-glass opacification. Similar patterns have been reported in other studies of adult RSV cases, where patterns described as bilateral interstitial infiltrates, which become alveolar and have subsequent lobar involvement or unilateral consolidation and ground-glass opacities,[23,24] have been described. These documented study findings contrast with other viral illnesses such as COVID-19, where the CXR features differ, and infiltrates that are ground glass and reticular, tending to favour the lower zones and peripheries, are described,[24,25] suggesting that RSV manifests uniquely on CXR imaging.

Study strengths and limitations

This study was conducted at two different sites, and a strength of this

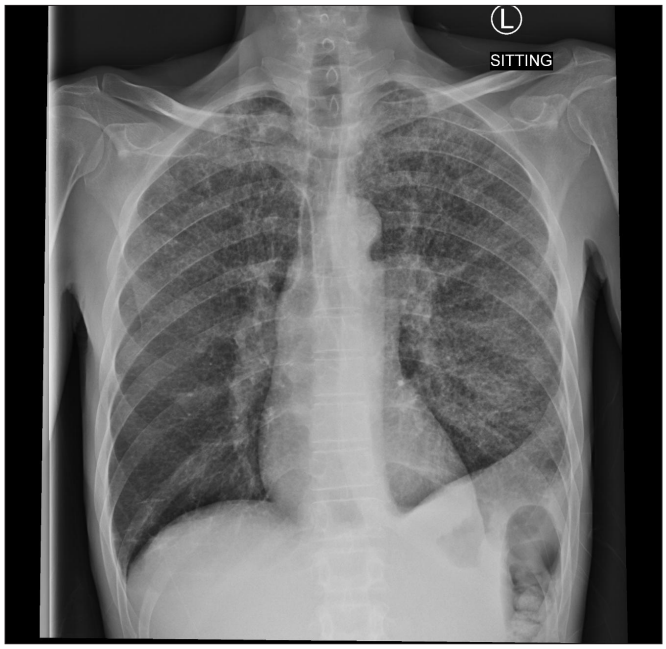

Fig. 2. Diffuse ground-glass opacification with nodular infiltrates in a patient with respiratory syncytial virus-associated severe respiratory illness with no other co-infections on this presentation.

Table 4. Laboratory findings in adults ≥ 18 years admitted with respiratory syncytial virus-associated severe respiratory illness, South Africa, 2022 - 2023

Laboratory parameter	*n* (%)*
WCC (× 109/L), median (range)	14.5 (4.6 - 31)
Elevated WCC (>11 × 109/L)	10/17 (59)
Sodium (mmol/L), median (range)	131 (124 - 139)
CRP (mg/L), median (range)	66 (43 - 332)
Elevated CRP (>30 mg/L)	5/8 (63)
Urea (>7 mmol/L), median (range)	8.08 (3.3 - 32.9)
Creatinine (>90 µmol/L), mean (SD)	159 (43)

WCC = white cell count; CRP = C-reactive protein; SD = standard deviation.
*Except where otherwise indicated.

study is that we were able to describe detailed clinical and radiographic features despite the small sample size. A few limitations are noted. We were reliant on information captured by primary healthcare practitioners, and certain risk factors, such as obesity, may have been underdocumented. The findings from this small study, especially the relationship between PTLD and RSV, will need to be studied in larger sample sizes.

Conclusion

In this description of RSV-associated SRI in hospitalised adults, we describe a unique epidemiology of RSV in our setting. Our patient profile appears to be younger, with HIV infection and PTLD as predominant underlying comorbidities, in contrast to what is described in other settings where cardiometabolic and traditional chronic respiratory diseases are more frequent. We also identify opportunities for improved antimicrobial stewardship and the need for accessible, affordable, rapid point-of-care tests for respiratory infections to avoid unnecessary antibiotic use. In addition, life-course vaccination strategies should be tailored to our unique burden of disease.

Data availability. The data sets generated and analysed during the present study are available from the corresponding author (NG) on reasonable request. Any restrictions or additional information regarding data access can be discussed with the corresponding author.
Declaration. The research for this study was done in partial fulfilment of the requirements for NG's MMed (Int Med) degree at Stellenbosch University. EI is a member of the editorial board
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