Infect Dis Ther (2025) 14:1075–1087
https://doi.org/10.1007/s40121-025-01148-9

ORIGINAL RESEARCH

Burden and Outcomes of Severe Lower Respiratory Tract Infections with Unknown Etiology: A Retrospective Observational Study on Epidemiological Trends Over an 8-Year Period (2016–2024)

Giovanni Scaglione · Marta Canuti · Martina Offer · Valentina Breschi · Antonio Piralla · Fausto Baldanti · Gabriele Del Castillo · Francesco Scovenna · Sabrina Buoro · Federica Morani · Danilo Cereda · Alessandra Bandera · Andrea Gori · Marta Colaneri

Received: February 6, 2025 / Accepted: March 27, 2025 / Published online: April 10, 2025

ABSTRACT

***Introduction*:** Severe lower respiratory tract infections often require hospitalization, but a significant proportion lack microbiological diagnosis, leading to challenges in management. This study aimed to compare clinical outcomes of S-LRTIs with unknown versus known bacteria or viral etiology in Lombardy, Italy.

***Methods*:** A retrospective study analyzed respiratory infection-related hospitalizations in Lombardy over 8 years (2016–2024) using patient discharge charts. Patients were categorized into four groups: bacterial, viral (non-COVID-19), COVID-19-related, and unknown etiology. Outcomes included length of stay, intensive care unit admissions, and intra-hospital mortality.

Giovanni Scaglione and Marta Canuti contributed equally to this work.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s40121-025-01148-9.

G. Scaglione · A. Gori · M. Colaneri (✉)
Department of Infectious Diseases, Luigi Sacco Hospital, University of Milan, Milan, Italy
e-mail: marta.colaneri@gmail.com

M. Canuti
Department of Veterinary and Animal Sciences, University of Copenhagen, 1870 Frederiksberg, Denmark

M. Offer · A. Gori · M. Colaneri
Department of Biomedical and Clinical Sciences, University of Milan, Milan, Italy

V. Breschi
Department of Electrical Engineering, Eindhoven University of Technology, 560 MB Eindhoven, The Netherlands

A. Piralla · F. Baldanti
Microbiology and Virology Department, Fondazione IRCCS Policlinico San Matteo, 27100 Pavia, Italy

F. Baldanti
Department of Clinical, Surgical, Diagnostic and Pediatric Sciences, University of Pavia, 27100 Pavia, Italy

G. Del Castillo · D. Cereda
Prevention Unit, General Directorate of Health, Lombardy Region, Milan, Italia

F. Scovenna
Department of Health Sciences, University of Milan, Milan, Italy

S. Buoro
Clinical Chemistry Laboratory, Hospital Papa Giovanni XXIII, Bergamo, Italy

F. Morani
Department of Biology, University of Pisa, 56126 Pisa, Italy

Temporal, seasonal, and age-specific trends were evaluated.

Results: Among 683,741 hospitalizations, 338,211 (49.5%) were of unknown etiology, showing a 12.3% intra-hospital mortality rate (41,627 deaths) and 4.0% intensive care unit admission rate (13,625 admissions). COVID-19-related hospitalizations had the highest intra-hospital mortality rate (22.0%, 36,446 deaths in 165,605 COVID-19-related hospitalizations) and number of intensive care unit admissions (14,725 admissions, 8.9% of COVID-19-related hospitalizations), while viral non-COVID-19 hospitalizations showed the lowest intra-hospital mortality rate (3.2%, 1114 deaths in 34,769 viral-non-COVID-19 hospitalizations) and shortest length of stay (11.9 days). Hospitalizations with unknown etiology were more common in minors (42,190 episodes, 57.6% of total in < 18 years) and elderly (358,534 episodes, 56.2% of total in > 75 years), especially during warm seasons. Post-pandemic years saw increased bacterial and viral hospitalizations alongside a reduced proportion of those without an unknown etiology.

Conclusions: Respiratory infection-related hospitalizations with unknown etiology are associated with distinct seasonal and demographic patterns, and poorer outcomes compared to viral non-COVID-19 hospitalizations. COVID-19 reshaped S-LRTI epidemiology and diagnostic approaches, highlighting the need for comprehensive pathogen panels and tailored management strategies, while promoting their expanded use. Future research should integrate detailed clinical data to improve understanding and outcomes of severe respiratory infections, especially in vulnerable populations.

Keywords: Lower respiratory tract infections; Epidemiology; Surveillance; Unknown etiology; COVID-19

Key Summary Points

Severe lower respiratory tract infections (S-LRTIs) are relevant drivers of morbidity and mortality, yet a large portion of cases lack a microbiological diagnosis, complicating clinical management.

This retrospective study compared clinical outcomes across S-LRTI hospitalizations with bacterial, viral (non-COVID-19), COVID-19-related, and unknown etiology in Lombardy, Italy, from 2016 to 2024.

This study analyzed 683,741 S-LRTIs, half (49.5%) of which were unknown etiology. These infections had high intra-hospital mortality (12.3%) and ICU admission rates (4.0%), with worse outcomes than viral non-COVID-19 cases.

Post-pandemic (after 2022), unknown etiology cases declined, while bacterial and viral non-COVID-19 infections increased. Children (<18) and elderly (>75) had the highest unknown etiology hospitalization rates, especially in warm seasons.

Findings highlight the dynamicity of respiratory syndromes' etiology, and the potential usefulness of molecular diagnostics to improve diagnostic yield in respiratory syndromes, particularly in vulnerable age groups.

INTRODUCTION

Lower respiratory tract infections (LRTIs) rank among the leading causes of death globally [1]. According to the World Health Organization (WHO), they are the 7th "biggest killer" in upper-middle-income (UMIC) countries and the first in low-income countries [2].

LRTIs are caused by different agents, such as viruses and bacteria, and comprise community-acquired pneumonia (CAP) and

A. Bandera
Department of Pathophysiology and Transplantation, University of Milano, Milan, Italy

A. Bandera
Infectious Diseases Unit, IRCCS Ca' Granda Ospedale Maggiore Policlinico Foundation, Milan, Italy

hospital-acquired pneumonia (HAP), acute bronchitis, infective chronic obstructive pulmonary disease (COPD) exacerbations, and bronchiolitis [3], with the severe cases (S-LRTI) frequently requiring hospitalization.

Specifically, CAP can be caused by viruses and typical or atypical bacteria, and it is a leading cause of death for both children and the elderly, with a case fatality rate that ranges between 9% and 17.5% in UMIC [4, 5]. Regarding COPD exacerbations, impacting patients older than 60 years, viruses are responsible for over 30% of cases [6], while bronchiolitis, frequently leading to hospitalization of children younger than 6 years old, has respiratory syncytial virus (RSV) as the most relevant cause [7].

Incidence, etiology, and outcomes of LTRIs vary significantly according to several populations, and environmental factors, including pathogen seasonality patterns, climate, vaccinations, and individual factors, age and smoking habits [8]. Moreover, the coronavirus disease 19 (COVID-19) pandemic further altered these patterns, affecting the incidence and severity of respiratory infections like those sustained by *Streptococcus pyogenes*, *Streptococcus pneumoniae*, Influenza virus, and RSV [9]. Particularly, the prolonged lockdown imposed during the first month of the severe acute respiratory syndrome virus 2 (SARS-CoV-2) epidemic heavily reduced the circulation of other pathogens too, causing the so-called "immunity debt", which resulted in the spike of several infectious diseases in the following years [10].

Despite the increasing use of molecular testing in hospital settings, a large proportion of S-LRTIs remains microbiologically undiagnosed [11]. PCR-based diagnostic panels frequently focus on well-known community pathogens, often excluding less frequent or highly diverse viruses [12], and empirical antibiotic use in outpatient settings can lower diagnostic yield in case of bacterial infections. As a result, LRTIs with unknown etiology, which refer to infectious respiratory conditions with no identified causative agent despite microbiological, radiological, and serological testing, are frequent [13]. Moreover, S-LRTIs with unknown etiology may have poorer outcomes due to the lack of targeted therapies [14].

While fully defining their epidemiological and clinical profiles is key, large-scale comparisons of outcomes in known versus unknown etiologies are limited by data collection challenges. Administrative databases, which compile comprehensive hospitalization records across broad populations, offer a standardized way to monitor large cohorts.

This study analyzed regional databases from Lombardy, northern Italy, which, with over 10 million inhabitants, largely exceeds the population of most European countries. Moreover, Lombardy was the European region hit the hardest during the early stages of the COVID-19 pandemic [15].

With this study, we firstly aimed to investigate whether S-LRTI with unknown etiology had worse clinical outcomes than those with known bacterial and viral etiology. Secondly, we pursued the description of the epidemiology, seasonality, and age-specific and temporal trends of S-LRTIs with both unknown and known bacterial and viral etiologies over the past 8 years (2016–2024) in Lombardy.

METHODS

Study Design and Inclusion Criteria

In this retrospective observational study, we included all the laboratory-confirmed or clinically diagnosed S-LRTI-related hospitalizations in Lombardy between May 1, 2016, and April 30, 2024. Demographic data of hospitalized patients and hospitalization outcomes were retrieved using Italian hospital discharge codes, according to the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) metrics. During the whole period, "warm" (May 1 to October 31) and "cold" (November 1 to April 30) seasons were considered to study seasonality.

Considered hospitalization-related clinical outcomes were: (i) length of stay (LOS), (ii) admission to the intensive care unit (ICU), and (iii) intra-hospital mortality.

Patients were excluded if they had a confirmed diagnosis of fungal or mycobacterial pulmonary disease or a confirmed diagnosis of conditions certainly not attributable to infections (e.g., pneumonia caused by chemical agents). Further details on the ICD-9-CM codes used, and its December 2020 update, are provided in the Online Data Supplement section (see web-only Supplementary Tables S1–S4).

Definitions

Four groups of S-LRTIs were defined: (i) bacterial S-LRTIs comprised CAP and HAP sustained by 21 different bacteria, empyema, and bacterial pleural effusion, (ii) viral, non-COVID-19, S-LRTI including RSV bronchiolitis, influenza A and B infections with pneumonia or other respiratory manifestation, and pneumonia caused by other respiratory virus (excluding molecular-confirmed cases of SARS-CoV-2), (iii) COVID-19-related S-LRTI consisted of pneumonia and acute respiratory distress syndrome (ARDS) diagnoses associated to SARS-CoV-2 infection, and (iv) S-LRTI with unknown etiology, which consisted of acute bronchiolitis, bronchitis, bronchopneumonia, and pneumonia presumably sustained by an infection but without a microbiological confirmation.

Diagnostic Methods

In the context of the Lombardy Region, diagnosis of S-LRTI varies significantly according to hospital location, size, and over time within the same center. The diagnosis of COVID-19-related S-LRTI was based on clinical, radiological, and epidemiological factors, supported by microbiological investigations on upper respiratory tract or LRT specimens using antigenic detection (mainly in emergency room setting) or using commercial molecular assays specific for SARS-CoV-2.

Regarding viral, non-COVID-19, S-LRTIs, clinical, radiological, and epidemiological guided the attending physician, and molecular assays including a panel of respiratory viruses such as influenza viruses (A, B, A/H1, A/H1 2009 pandemic virus, A/H3), respiratory syncytial virus A and B, adenoviruses A-G, enteroviruses, parainfluenza viruses subtypes 1–4, human metapneumovirus A/B, rhinoviruses, human coronaviruses (NL63/229E/OC43/HKU1) were used for the diagnosis. This extensive panel was commonly and widely used according to clinical suspicion and regional indications on respiratory pathogens' surveillance provided at that time.

For bacterial pathogens, the above-mentioned patient's features were also guiding the diagnostic process, with a wider array of antigenic and molecular methods available for different biological materials (e.g., urinary antigens for *Legionella* spp. and *Streptococcus pneumoniae,* or molecular testing for bacterial and viral pathogens on bronchoalveolar lavage material) according to each individual center's needs and possibilities at any given time. An example of widespread molecular testing panel for bacterial pathogens in Lombardy region detects: *Chlamydia pneumoniae* DNA, *Mycoplasma pneumoniae* DNA, *Legionella pneumophila* DNA, *Haemophilus influenzae* DNA, *Streptococcus pneumoniae* DNA, *Bordetella pertussis* DNA, *Bordetella parapertussis* DNA.

Outcomes of the Study

The primary outcome of this study was to compare the epidemiology and hospitalization-related clinical outcomes of S-LRTIs with unknown versus known viral or bacterial etiology.

The secondary outcomes were: (i) to investigate the S-LRTIs epidemiology and outcomes across different seasons and age groups (0–6, 7–17, 18–59, 60–74, and over 74 years old), and (ii) to study the temporal trends of outcomes for the four S-LRTIs groups over time.

Statistical Analyses

Continuous variables are presented as median and interquartile ranges (IQR), while categorical variables are presented as percentages.

Categorical values of outcomes for the whole study period were compared using the Chi-square test among the four infection groups. Furthermore, the cumulative seasonal median values for bacterial and viral hospitalization-related outcomes in the years 2016–2024 were depicted with violin plots and compared to those of unknown etiology S-LRTI (reference value) using the Mann–Whitney test. Lastly, the cumulative distributions of events for each S-LRTI in different age group (0–6, 7–18, 19–59, 60–74, and > 75 years) were graphically represented with scatter plots for both "warm" and "cold" seasons. Data were analyzed using R software, version 4.3.3, and MATLAB software, version 2023a. Statistical significance was accepted at the 5% level.

RESULTS

A total of 683,741 hospital admissions recorded as S-LRTIs were identified in the study period, mostly in males (387,009, 56.6%) with a median age of 68.7 [65.1; 70.8] years. Overall, the median LOS was 15.3 [13.1; 17.0] days (Table 1). Unknown etiology S-LRTI was observed in nearly half of the cases (338,211, 49.5%) and was associated with 12.3% intra-hospital mortality (41,627 deaths) and 4.0% ICU admission rate (13,625 admissions).

Outcomes and Seasonality

Over the whole period, bacteria and COVID-19-related S-LRTIs groups showed similar rates of hospitalizations and ICU admissions. In contrast, intra-hospital mortality was higher for COVID-19 (36,446, 22.0%) than for bacteria (20,143, 13.9%) infections. Viral, non-COVID-19 S-LRTIs included the youngest patients (32.7 [21.4; 39.6] years), the lowest intra-hospital mortality (1114, 3.2%), and the shortest median LOS (11.9 [8.8; 15.4] days). ICU admission and intra-hospital mortality rates were significantly different among the four LRTIs groups, with COVID-19-related S-LTRIs having the highest values for both (Table 1).

Figure 1 shows the distribution of medians obtained for all considered outcomes in each season over the whole period. We observed statistically significant differences in the median

Table 1 Characteristics and outcomes of the study population, categorized by the etiology of the diagnosed respiratory syndrome

	Bacterial S-LRTI	Viral, non-COVID-19, S-LRTI	Unknown etiology S-LRTI	COVID-19-related S-LRTI	Total	*p* value
Number of hospitalizations	145,156.0	34,769.0	338,211.0	165,605.0	683,741.0	
Male gender (%)	84,371.0 (58.1%)	18,651.0 (53.6%)	182,510.0 (54.0%)	101,477.0 (61.3%)	387,009.0 (56.6%)	
Median age (years, [IQR])	70.1 [69.1; 71.3]	32.7 [21.4; 39.6]	69.2 [65.6; 70.6]	72.9 [69.3; 78.5]	68.7 [65.1; 70.8]	
Median LOS (days, [IQR])	16.9 [16.3; 18.1]	11.9 [8.8; 15.4]	13.8 [13.0; 14.0]	17.2 [16.5; 18.2]	15.3 [13.1; 17.0]	
Number of ICU admissions (%)	13,896.0 (9.6%)	3036.0 (8.7%)	13,625.0 (4.0%)	14,725.0 (8.9%)	45,282.0 (6.6%)	0.521
Intra-hospital deaths (%)	20,143.0 (13.9%)	1114.0 (3.2%)	41,627.0 (12.3%)	36,446.0 (22.0%)	99,330.0 (14.5%)	0.00098

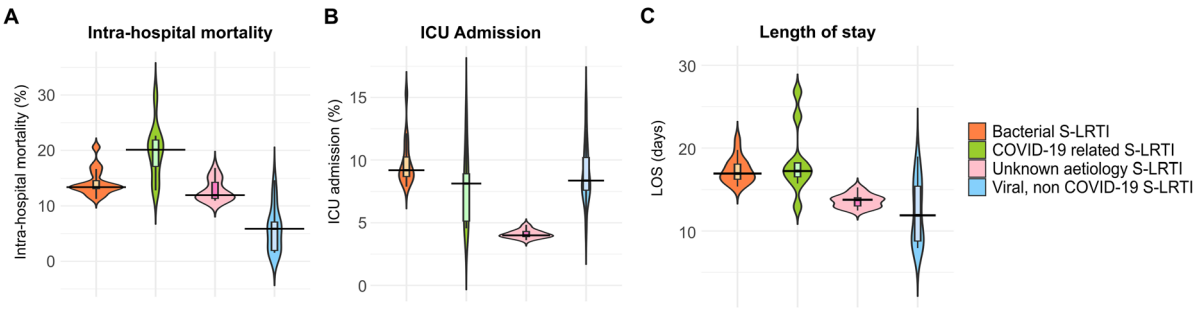


Fig. 1 Violin plots illustrating the distribution and median values of seasonal mortality (**A**, *upper*), ICU admissions (**B**, *middle*), and mean LOS (**C**, *lower*) of each S-LRTI group for the 2016–2024 period. *S-LRTI* Severe lower respiratory tract infection

Table 2 Comparisons of the median values of cumulative distributions for intra-hospital seasonal mortality rates, ICU admission rates, and LOS across the evaluated seasons comparing respiratory syndromes with unknown etiology and those with confirmed bacterial or viral detections

	Unknown etiology S-LRTI (reference value)	Bacterial S-LRTI	Viral, non-COVID-19, S-LRTI	COVID-19-related S-LRTI
Mean LOS (median; [IQR])	13.8 [13.0, 14.0]	16.9 [16.3, 18.1]	11.9 [8.8, 15.4]	17.2 [16.5, 18.2]
p value	//	< 0.001	0.3558	< 0.001
ICU admission rate (median; [IQR])	4.0% [3.9; 4.3]	9.2% [8.7; 10.2]	8.4% [7.6; 10.2]	8.1% [5.1; 8.9]
p value	//	0.137	< 0.001	0.095
Mortality rate (median; [IQR])	12.0% [11.4; 14.3]	13.4% [13.1; 14.6]	5.9% [1.9; 7.1]	20.1% [17.1; 21.9]
p value	//	0.48	< 0.001	< 0.001

distributions of mortality and ICU admission rates for unknown etiology S-LRTI ($p < 0.001$) (Table 2). Unknown etiology S-LRTI demonstrated lower intra-hospital mortality compared to COVID-19-related S-LRTIs, but higher than other viral S-LRTIs (Fig. 1A). Differently, unknown etiology S-LRTIs were associated with lower ICU admission rates compared to those of the other three groups of S-LRTIs (Fig. 1B). Additionally, unknown etiology S-LRTI was associated with a significantly shorter LOS compared to COVID-19, and bacteria-related hospitalization ($p < 0.001$, Fig. 1C).

Age-specific data for the considered clinical outcomes, divided across the "warm" and "cold" seasons, are shown in Fig. 2.

A total of 73,291 hospitalizations for S-LRTI were observed in the pediatric population (10.7% of total), most among 0–6 years old children (65,191, 88.9%). The cumulative number of intra-hospital deaths each year in the age group < 18 years was very low (minimum 2, maximum 9 intra-hospital deaths).

In the 0–6 years age bracket, S-LRTI of unknown etiology represented the highest number of hospitalizations (37,454, 57.5%), followed by viral, non-COVID-19 S-LRTIs (21,727, 33.3%), particularly prevalent in the "cold" seasons. Bacterial and COVID-19-related S-LRTIs caused less hospitalizations (5765 and 245, 8.8% and 0.4%, respectively), but were associated with higher in-hospital mortality (22 and 2, 0.4% and 0.8%,

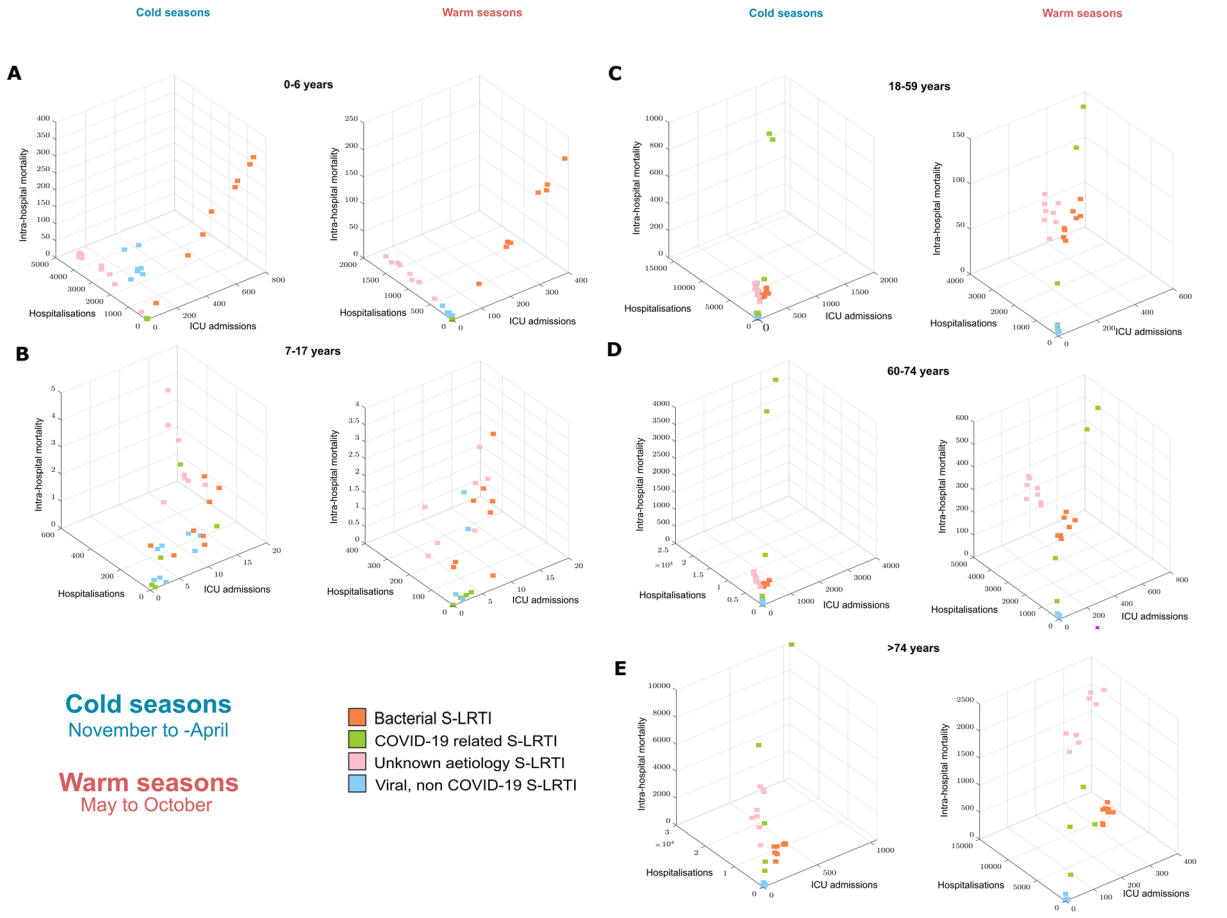


Fig. 2 Tentative plots representing the distribution of hospitalization outcomes across age groups 0–6 years (**A**), 7–17 years (**B**), 18–59 years (**C**), 60–74 years (**D**), and > 75 years (**E**) across two time periods: "Cold" Season (November to April of the following year) on the left, and "Warm" Season (May to October) on the right, for the years 2016–2024. *ICU* intensive care unit

respectively), and ICU admission rates (446 and 29, 7.7% and 11.8%, respectively) as shown in Fig. 2A.

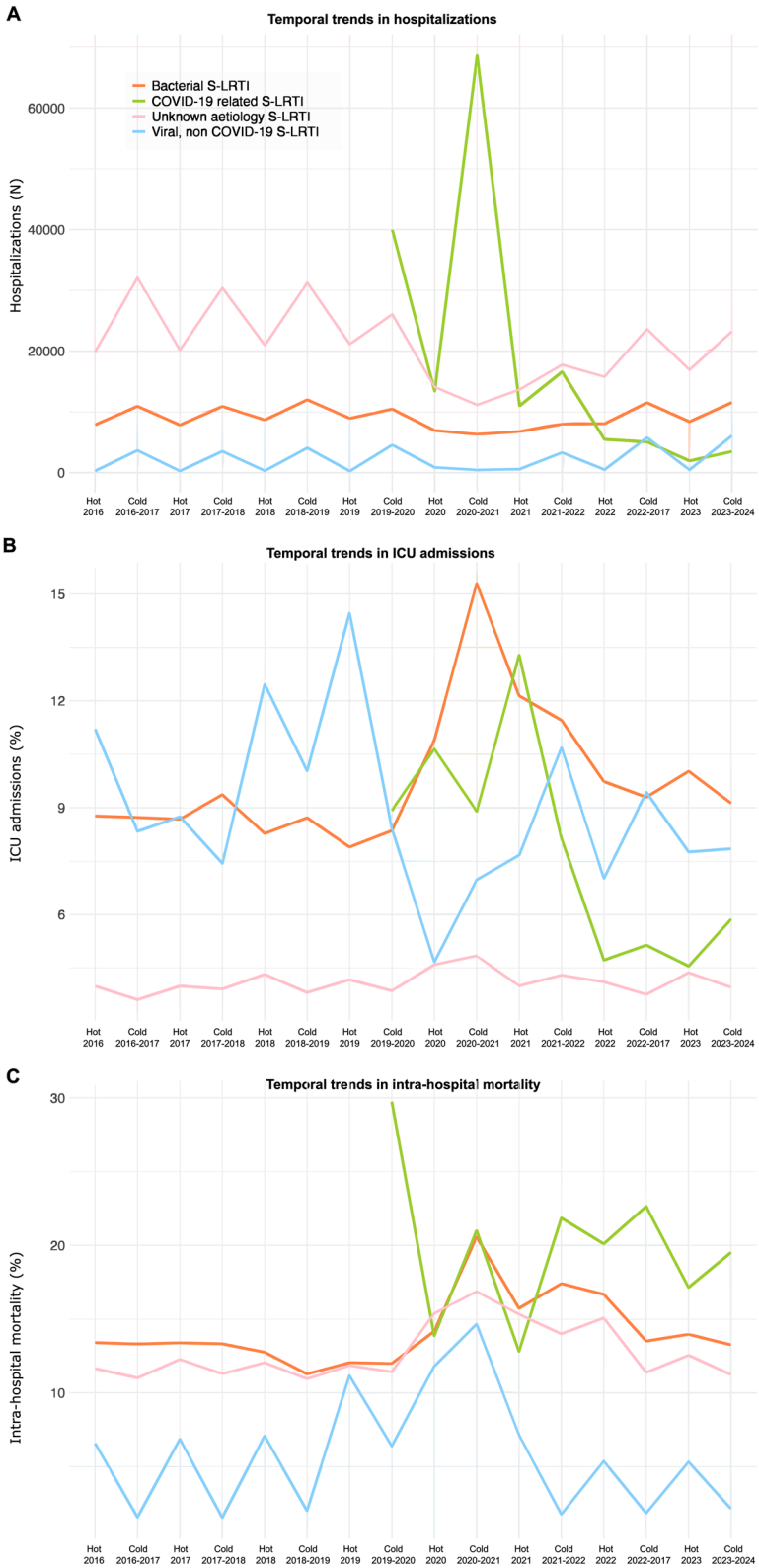
Conversely, the group 7–17 years counted 8100 patients (11.1%). In this age group, unknown and bacterial etiology S-LRTIs were the most frequently observed (2136 and 4736, 26.4% and 58.5%, respectively) and adverse outcomes were rare (Fig. 2B).

Most detected hospitalizations, and hospitalization-related outcomes, were in the adult populations (18–59, 60–75, and > 75 years groups, Fig. 2C–E) with 610,450 inpatients (89.3%). COVID-19-related S-LRTIs had the highest overall mortality in both "cold" and "warm" seasons, and this was particularly true for the 18–59 and 60–74 age groups (Fig. 2C, D).

Differently, we noticed a greater degree of heterogeneity in the etiologies of S-LRTIs in patients > 75 years, with numerous hospitalizations, and fewer ICU admissions. In this group, unknown etiology S-LRTIs remains the most represented, particularly in the "warm" seasons, where their prevalence surpassed the one of COVID-19-related S-LRTIs (Fig. 2E).

Temporal Trends

During the first pandemic period (2019–2022), COVID-19 was the most frequent cause of


A
Temporal trends in hospitalizations
Bacterial S-LRTI
COVID-19 related S-LRTI
Unknown aetiology S-LRTI
Viral, non COVID-19 S-LRTI
Hospitalizations (N)
60000
40000
20000
0
B
Temporal trends in ICU admissions
ICU admissions (%)
15
12
9
6
C
Temporal trends in intra-hospital mortality
Intra-hospital mortality (%)
30
20
10
Hot 2016
Cold 2016-2017
Hot 2017
Cold 2017-2018
Hot 2018
Cold 2018-2019
Hot 2019
Cold 2019-2020
Hot 2020
Cold 2020-2021
Hot 2021
Cold 2021-2022
Hot 2022
Cold 2022-2017
Hot 2023
Cold 2023-2024

◂**Fig. 3** Temporal trends for total number of hospitalizations (**A**, *top*), ICU admissions (**B**, *middle*), and intra-hospital mortality (**C**, *bottom*). Warm and Cold on the *x*-axis represent the "Warm" and "Cold" seasons as identified in the Methods section ("Warm season" covering the May 1 to October 31 period and "Cold season" for the November 1 to April 31 period)

hospitalizations and outcomes, remaining relevant in subsequent years. Bacterial, viral, and unknown etiology S-LRTI cases were lowest from May 2020 to May 2022, then returned to pre-pandemic levels for viral and bacterial S-LRTI. Notably, viral non-COVID-19 S-LRTI hospitalizations peaked in 2022–2024, coinciding with the lowest number of unknown etiology S-LRTI diagnoses, excluding the first two pandemic years (Fig. 3A).

In the same 2022–2024 period, we also observed the highest number of ICU admissions for bacterial and viral, non-COVID-19 causes, but the hospitalizations total grew more, resulting in reduced admission rates (Fig. 3B). Patterns of intra-hospital mortality rates were alike, recording the highest mortality rates for viral, non-COVID-19 S-LRTI and bacterial etiology S-LRTI in the first pandemic period (2019–2021), decreasing in the following two (2022–2024) years (Fig. 3C). Consistently, ICU admissions and intra-hospital deaths for unknown etiology S-LRTI were lower in the post-pandemic period, with similar rates compared to the years before the COVID-19 pandemic (Fig. 3B, C).

Lastly, the proportion of hospitalizations for unknown etiology S-LRTI significantly changed over time ($p<0.001$) and this was accompanied by a significant change in the COVID-19-related ($p<0.001$) and bacterial ($p=0.042265$) S-LRTI hospitalizations (Table 3). When comparing the pre-pandemic pooled proportion of unknown etiology S-LRTI hospitalizations (154,751 hospitalizations over 3 years, 68.8% of the total) with the data collected from the 2019–2020 "cold" season onwards (183,460 hospitalizations over 5 years, 40.0% of total), the numbers differed significantly ($p<0.0001$).

DISCUSSION

This study showed that approximately half of the S-LRTI hospitalizations recorded in Lombardy in the years 2016–2024 were of unknown etiology. Unknown etiology S-LRTIs were associated with high median age and high in-hospital mortality rates, lower than those related to COVID-19 but higher than those caused by other viruses, with overall low ICU admission rates. These differences in outcomes between the unknown etiology S-LRTI group and the others underscore the distinct clinical characteristics of patients in this group. These findings are consistent with prior studies which also report a significant proportion of S-LRTIs with an unknown etiology [16].

Post-pandemic, unknown-etiology S-LRTI declined, likely due to broader molecular testing (including SARS-CoV-2) becoming more available, even in smaller hospitals. In Lombardy, access to next-generation sequencing was expanded in 2022 [17], and a regional council resolution launched a program for respiratory syndrome identification in emergency departments, further increasing diagnostic efforts [18].

Nonetheless, current diagnostic panels tend to remain mostly focused on the most relevant pathogens, and this aspect, combined with the widespread use of antibiotics before hospital admission, contributes to reduced diagnostic sensitivity [10, 19]. Furthermore, the current standard for diagnosing viral infections relies on average one microbiological diagnostic technique rather than a combination of them, which has shown improved detection rates of difficult-to-diagnose infections such as RSV in adults [20].

Lastly, the need to improve diagnostics in viral and bacterial S-LRTIs is crucial for infection control practices, in order to rapidly assess which patients require contact, droplets, and airborne isolation measures, with the aim of reducing intra-hospital transmission of respiratory infections.

Interestingly, unknown etiology S-LRTIs had lower ICU admissions than confirmed bacterial or viral cases, especially COVID-19, which showed the highest ICU and mortality rates in

Table 3 Number of hospitalizations per year for each S-LRTI group over the 2016–2024 period

Period (year)	Bacterial S-LRTI	(%)	COVID-19 related S-LRTI	(%)	Unknown etiology S-LRTI	(%)	Viral, non-COVID-19 S-LRTI	(%)
2016–2017	18,790.0	25.2	//	//	51,933.0	69.6	3915.0	5.3
2017–2018	18,751.0	25.6	//	//	50,600.0	69.2	3772.0	5.2
2018–2019	20,673.0	26.8	//	//	52,218.0	67.6	4364.0	5.6
2019–2020	19,399.0	17.4	39,968.0	35.9	47,203.0	42.4	4793.0	4.5
2020–2021	13,259.0	10.9	82,034.0	67.3	25,245.0	20.7	1287.0	1.1
2021–2022	14,781.0	19.0	27,614.0	35.5	31,452.0	40.5	3869.0	5.0
2022–2023	19,564.0	25.8	10,545.0	13.9	39,398.0	52.0	6245.0	8.2
2023–2024	19,939.0	27.7	5444.0	7.5	40,162.0	55.7	6524.0	9.1
p value	0.042265		< 0.0001		< 0.0001		0.565	

elderly patients with comorbidities [21, 22]. This could reflect the heterogeneous nature of unknown etiology cases—some milder, some fulminant or rare, and some in severely debilitated patients for whom intensive diagnostics and care were not pursued.

Age influenced outcomes, with adults over 18 showing the highest mortality and ICU admission rates for S-LRTIs, especially COVID-19-related. These findings align with evidence on age-related immune decline and comorbidities. Patients over 75 faced even higher risks, often compounded by reduced baseline performance status limiting ICU access [23]. Older adults with unknown etiology pneumonia thus represent a particularly vulnerable group requiring targeted interventions. Children under six often presented with unknown etiology S-LRTI but had lower intra-hospital mortality than adults. This aligns with findings that younger populations in UMICs typically have milder disease, possibly due to distinct immune responses and fewer comorbidities [24]. Unknown etiology S-LRTI in this group showed low mortality and ICU rates, similar to virus-related hospitalizations, suggesting some cases may involve viruses not detected by standard diagnostic panels.

Seasonal variations were also found, particularly regarding viruses other than SARS-CoV-2, practically absent in the "warm" season but surging during the November–April period, especially among young children, where they represented the most common S-LRTIs diagnosis.

Temporal trends also highlighted a resurgence of bacteria, and viruses other than SARS-CoV-2 following the peak COVID-19 pandemic years. This likely reflects the phenomenon of "immunity debt," in which reduced exposure to pathogens during pandemic restrictions resulted in a rebound of infectious diseases once restrictions were lifted. Overall, mortality and ICU admission rates were the highest for all four groups during the peak pandemic period (2020–2021), likely reflecting the unsustainable pressure faced by Lombardy's healthcare system at that time.

This study leveraged administrative databases, enabling the inclusion of a large population and allowing meaningful comparisons. However, some limitations warrant consideration. Firstly, some technical difficulties and inconsistencies in diagnostic coding precluded the inclusion of co-infection data. Secondly, large numbers, and the use of discharge codes are inherently linked to the possibility of selecting the same patient two or more times. Thirdly, the inclusion of acute exacerbation of COPD cases within the unknown etiology S-LRTI group—associated with intra-hospital mortality rates below 1%—likely mitigated the overall in-hospital mortality rate for this group. This could obscure

differences between, for example, unknown etiology and bacterial CAP, and other categories.

Finally, the reliance on ICD coding introduces potential inaccuracies in diagnosis classification and limits the clinical granularity of the data, constraining the interpretation of observed outcomes. Nonetheless, the study's objective was not to provide precise prognostic estimates but to capture an evolving picture of S-LRTI epidemiology and diagnostic trends in a densely populated European region.

CONCLUSIONS

This study underscores the ongoing challenges of S-LRTIs across diverse patient populations. The variability in clinical outcomes highlights the need for more comprehensive diagnostic panels and improved management approaches tailored to specific age groups and seasonal trends. The COVID-19 pandemic re-shaped the epidemiology, and diagnostic approaches to respiratory syndromes, likely increasing diagnostic yield in viral cases. However, future research integrating detailed clinical and laboratory data are essential to better understand S-LRTI outcomes, particularly among older adults and young children.

ACKNOWLEDGEMENTS

The authors express their deepest gratitude to all the healthcare workers and professionals in the Lombardy region for their unwavering dedication and tireless efforts in combating the COVID-19 pandemic. Their commitment to patient care and public health during this unprecedented time has been an inspiration and an invaluable contribution to this study.

Author Contributions. Conceptualization: Giovanni Scaglione, Marta Canuti, Marta Colaneri. Data Curation: Giovanni Scaglione, Marta Canuti. Writing—Original Draft: Giovanni Scaglione, Marta Canuti. Formal Analysis: Martina Offer, Valentina Breschi. Visualization: Marta Colaneri, Martina Offer, Valentina Breschi. Methodology: Martina Offer, Antonio Piralla, Fausto Baldanti. Writing—Review & Editing: Antonio Piralla, Fausto Baldanti, Marta Colaneri. Data Acquisition: Gabriele Del Castillo, Francesco Scovenna, Sabina Buoro, Federica Morani. Project administration: Danilo Cereda, Andrea Gori, Alessandra Bandera. Supervision: Marta Colaneri, Danilo Cereda, Andrea Gori.

Funding. No funding or other sources of support were received for the idealization or completion of this study. The payment of the Rapid Service Fee was funded by the authors through European Union funds, fund number PR-0452; project code C43C22002410002.

Data Availability. The datasets generated during and/or analyzed during the current study are available from the corresponding author upon reasonable request.

Declarations

Conflict of Interest. Giovanni Scaglione, Marta Canuti, Matina Offer, Valentina Breschi, Antonio Piralla, Fausto Baldanti, Gabriele Del Castillo, Francesco Scovenna, Sabrina Buoro, Federica Morani, Danilo Cereda, Alessandra Bandera, Andrea Gori, and Marta Colaneri have no competing interests to declare.

Ethical Approval. This study was conducted in accordance with the principles of the Declaration of Helsinki. According to Italian law, studies using retrospective aggregated data from administrative databases that do not involve direct access by investigators to individual patient data do not require approval, notification from an Ethics Committee/institutional review board, or patient informed consent.

REFERENCES

1. Welte T, Torres A, Nathwani D. Clinical and economic burden of community-acquired pneumonia among adults in Europe. Thorax. 2012;67:71–9.

2. WHO. https://www.who.int/news-room/fact-sheets/detail/the-top-10-causes-of-death. Accessed 30 Dec 2024.

3. Feldman C, Shaddock E. Epidemiology of lower respiratory tract infections in adults. Expert Rev Respir Med. 2019;13:63–77.

4. Kliegman RM, Sandora T, Sectish T. Nelson Textbook of Pediatrics, 20st ed. 2015, part XIX, section 2, chapter 392, page 1474.

5. Shi T, Denouel A, Tietjen AK, Lee JW, Falsey AR, Demont C, et al. Global and regional burden of hospital admissions for pneumonia in older adults: a systematic review and meta-analysis. J Infect Dis. 2020;222:S570–6.

6. Mohan A, Chandra S, Agarwal D, Guleria R, Broor S, Gaur B, et al. Prevalence of viral infection detected by PCR and RT-PCR in patients with acute exacerbation of COPD: a systematic review. Respirology. 2010;15:536–42.

7. Soni A, Kabra SK, Lodha R. Respiratory syncytial virus infection: an update. Indian J Pediatr. 2023;90:1245–53.

8. Sharma BB, Singh S, Sharma KK, Suraj KP, Mahmood T, Samaria KU, et al. Methodology of seasonal waves of respiratory disorders survey conducted at respiratory outpatient clinics across India. Lung India. 2020;37:100–6.

9. Principi N, Autore G, Ramundo G, Esposito S. Epidemiology of respiratory infections during the COVID-19 pandemic. Viruses. 2023;15:1160.

10. Cohen R, Levy C, Rybak A, Angoulvant F, Ouldali N, Grimprel E. Immune debt: recrudescence of disease and confirmation of a contested concept. Infect Dis Now. 2023;53: 104638.

11. Bordley WC, Viswanathan M, King VJ, Sutton SF, Jackman AM, Sterling L, et al. Diagnosis and testing in bronchiolitis. Arch Pediatr Adolesc Med. 2004;158:119.

12. Boukli N, Flamand C, Chea KL, Heng L, Keo S, Sour K, et al. One assay to test them all: multiplex assays for expansion of respiratory virus surveillance. Front Med (Lausanne). 2023;10:1161268.

13. Malakounidou E, Tsiri P, Theochari E, Koulousousa E, Karampitsakos T, Tzouvelekis A. Lower respiratory tract infections treatment recommendations: an overview. Pneumon. 2023;36:1–11.

14. Rubinstein E, Carbon C, Rangaraj M, Ignacio Santos J, Thys J-P, Veyssier P. Lower respiratory tract infections: etiology, current treatment, and experience with fluoroquinolones. Clin Microbiol Infect. 1998;4(Suppl 2):S42–50.

15. Storti L, Torpey J, Dagnes J, Filandri M, Lyons J. A tale of two epicentres: Lombardy and New York City at the outbreak of the Coronavirus pandemic. Modern Italy. 2022;27:155–80.

16. Shoar S, Musher DM. Etiology of community-acquired pneumonia in adults: a systematic review. Pneumonia (Nathan). 2020;12:11.

17. Regione Lombardia. Deliberazione XI/6989: Rete regionale dei servizi di medicina di laboratorio: approvazione del modello organizzativo per il potenziamento delle attività analitiche di sequenziamento di nuova generazione (Next Generation Sequencing - NGS). Milan: 2022.

18. Regione Lombardia. Deliberazione XII/63: Identificazione della rete di laboratori clinici per il supporto al PanFlu 2021–2023 e attivazione del sistema di sorveglianza delle sindromi respiratorie e influenzali in pronto soccorso. Milan: 2023.

19. Abu-Raya B, Viñeta Paramo M, Reicherz F, Lavoie PM. Why has the epidemiology of RSV changed during the COVID-19 pandemic? EClinicalMedicine. 2023;61: 102089.

20. Ramirez J, Carrico R, Wilde A, Junkins A, Furmanek S, Chandler T, Schulz P, Hubler R, Peyrani P, Liu Q, Trivedi S, Uppal S, Kalina WV, Falsey AR, Walsh EE, Yacisin K, Jodar L, Gessner BD, Begier E. Diagnosis of respiratory syncytial virus in adults substantially increases when adding sputum, saliva, and serology testing to nasopharyngeal swab RT-PCR. Infect Dis Ther. 2023;12(6):1593–603.

21. Maruotti A, Jona-Lasinio G, Divino F, Lovison G, Ciccozzi M, Farcomeni A. Estimating COVID-19-induced excess mortality in Lombardy. Italy Aging Clin Exp Res. 2022;34:475–9.

22. Häder A, Köse-Vogel N, Schulz L, Mlynska L, Hornung F, Hagel S, et al. Respiratory infections in the aging lung: implications for diagnosis, therapy, and prevention. Aging Dis. 2023;14:1091–104.

23. Escudero-Acha P, Leizaola O, Lázaro N, Cordero M, Gomez-Acebo I, González-Castro A, et al. Age as a limiting factor of admission to an intensive care unit. Med Intensiva. 2021;45:e47–9.

24. Kyu HH, Stein CE, Boschi Pinto C, Rakovac I, Weber MW, Dannemann Purnat T, et al. Causes of death among children aged 5–14 years in the WHO European Region: a systematic analysis for the Global Burden of Disease Study 2016. Lancet Child Adolesc Health. 2018;2:321–37.