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# Physiological Burden of Cardiometabolic and Respiratory Comorbidities in Patients with SARI-Related Symptoms: A Cross-Sectional Analysis of Diabetes Mellitus, Documented Heart Failure, Bronchial Asthma, Age, Sex, and Symptom Phenotypes

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## Abstract

**Background:** The physiological state can modify disease expression and burden for many respiratory syndromes. Severe acute respiratory infection (SARI) is one of these syndromes. The presence of chronic respiratory and cardiometabolic conditions can alter the immune response and increase the host's vulnerability to respiratory infection. This study aimed to identify the distribution of SARI symptom-related phenotypes and to assess the degree of their association with bronchial asthma; chronic obstructive pulmonary disease; diabetes mellitus; documented heart failure; and coronary heart disease by age, gender, and multimorbidity burden. Methods: A cross-sectional study analyzed 222 twin-sampling clinical records for chronic diseases and SARI symptoms. The description and classification of symptoms were standardized using binary indicators and were classified as fever, cough, or cough and fever. Statistical analyses were performed to assess the associations with the symptom phenotypes. **Results:** The average age of the study population was 52.8 +/- 23.4 years, and 53.2% were women. The most frequent symptoms were cough and fever, which were found in 199 (89.6%) of study participants. Diabetes mellitus and heart failure were the most frequent chronic diseases, and the most frequent overlap was 142 (64%) with diabetes mellitus and documented heart failure. Bronchial asthma was inversely associated with the cough-and-fever symptom (adjusted OR 0.22, 95% CI 0.08 - 0.62; $p = 0.004$). The relationship between age and the count of comorbidities was positive (Spearman rho = 0.304; $p < 0.001$), and there was no relationship between age and the cough and fever symptoms.

**Keywords:** SARI; diabetes mellitus; documented heart failure; bronchial asthma; multimorbidity; cough; fever.

## 1. Introduction

The recognition of pathogen and host factors makes severe acute respiratory infection (SARI) an important clinical and epidemiological syndrome. The WHO definition of surveillance includes acute respiratory illness with fever and cough of recent onset that necessitates hospitalization. Thus, in the surveillance of respiratory diseases, the combined cough and fever symptom pattern is of clinical significance [1]. That being said, the clinical presentation of a respiratory infection may be affected by many biologically determined factors such as age, sex, and the status of the nervous and immune systems, as well as the presence of cardiopulmonary disease and respiratory illness [2].

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Chronic diseases influence the presentation of respiratory infection. For instance, the glycation of immune and other cells, along with chronic inflammation in diabetes, may impair many respiratory antiviral and immune responses. This is of particular concern for respiratory infections, as the rapid response of the airway and lung immune systems is the primary defense against infection in the lungs [3,4]. Likewise, chronic heart failure may restrict the body's ability to respond to infection and inflammation, resulting in advanced hypoxia and heart failure [5].

SARI presentation is influenced by respiratory comorbidities. Of particular concern are bronchial asthma and chronic obstructive pulmonary disease. Both of these alter airway reactivity, mucus, cough reflex sensitivity, and barrier function. Exacerbation of bronchial asthma is a common presentation of a viral respiratory infection. Furthermore, chronic airway disease may alter the presentation of systemic illness, which is characterized by fever and acute inflammation [6,7]. Thus, the assessment and management of respiratory and cardiometabolic diseases ought to be considered as integrated physiological systems rather than isolated clinical entities [8].

One major challenge in analyzing clinical datasets stems from the fact that patients commonly present with multiple chronic conditions. It is known that a patient with only diabetes mellitus is going to be physiologically different than a patient with diabetes mellitus with heart failure and bronchial asthma. Multimorbidity may be characterized by a cumulative burden of metabolic, vascular, inflammatory, and pulmonary susceptibilities [9].

Because of this, this study examined both individual chronic disease components and the patterns of disease overlap. The aim was to explain the symptom phenotypes of SARI and determine the relationship with chronic disease, the overlap of comorbidities, age, and sex.

## 2. Materials and Methods

### 2.1 Study design and dataset

This study employed a cross-sectional design and used clinical records that listed chronic diseases, symptoms related to SARI, sex, and age. Because the information was originally arranged as pasted blocks of chronic diseases/symptoms and demographics, we performed row-wise matching up to the smaller complete set of paired rows and obtained 222 records for analysis. This method of matching prevents duplication of records and maintains one-to-one correspondence of chronic disease status, symptoms, sex, and age.

### 2.2 Variable standardization and coding

Entries for chronic disease were formatted before the statistical analysis was done. Irregular spacing, inconsistent punctuation, and differing abbreviations were all standardized and cleaned. For example, variants such as combinations of multiple diseases, such as Diabetes mellitus + documented heart failure (DMI-DHF), Diabetes mellitus + documented heart failure + bronchial asthma (DMI–DHF–BA), and Diabetes mellitus + bronchial asthma (DMI -BA), were all standardized and created as binary disease indicators. Multiple entries for multiple chronic diseases were included for patients with multiple chronic diseases. Patients coded as No were the reference group with no chronic diseases recorded.

**Table 1. Standardized coding dictionary used for manuscript analysis**

| Original code in dataset | Standardized manuscript term | Analytical coding |
|---|---|---|
| DMI / DM | Diabetes mellitus | Binary: present/absent |
| DHF | Documented heart failure | Binary: present/absent |
| BA | Bronchial asthma | Binary: present/absent |
| CRD | Chronic respiratory disease | Binary: present/absent |
| CHD | Coronary heart disease | Binary: present/absent |
| No | No recorded chronic disease | Reference category |

### 2.3 Statistical analysis

For the categorical variables, we examined frequencies and percentages. Age, a continuous variable, was summarized as mean and standard deviation, as well as median and interquartile range. Sex differences in age were examined using an independent-samples method. All other categorical variables were examined assuming a chi-square distribution, and Fisher's exact tests were used when cell counts were smaller than 5. Indicators of chronic disease were stratified against SARI symptom phenotypes. To estimate crude and adjusted odds ratios for the cough-and-fever phenotype, logistic regression was employed. Age and comorbidity count were examined for correlation using the Spearman method. A two-sided p-value less than 0.05 was considered statistically significant.

## 3. Results

### 3.1 Baseline demographic and clinical characteristics

The paired analytic dataset comprised 222 patients with comprehensive chronic condition/symptom and demographic data. It consisted of 118 females (53.2%) and 104 males (46.8%). The mean age of patients was 52.8 years (SD 23.4), suggesting the majority of the patients were adults or older adults, and the age range was quite diverse and broad. There was little to no discernible difference in age by sex. This suggested that, for baseline age structure, there were little to no differences between the male and female groups and that the male and female groups were likely comparable (Table 2).

### 3.2 Distribution of SARI symptom phenotypes

The most common symptoms were cough plus fever, which were found in 199 patients (89.6%). Presentation with fever alone was noted in 21 patients (9.5%). Cough presentation alone was seen in 2 patients (0.9%). The counts show that, in general, most records showed the full SARI-compatible symptom phenotype. Isolated symptom phenotypes were noted less frequently. Due to the small number of records that stated cough only, the results of the statistical comparisons associated with those records should be interpreted with caution (Table 3 and Figure 1).

### 3.3 Chronic disease indicators across SARI symptom phenotypes

Statistically significant associations with SARI symptom phenotype were observed for the absence of a recorded chronic disease ($P = 0.039$), diabetes mellitus ($P = 0.023$), documented heart failure ($P = 0.015$), and bronchial asthma ($P < 0.001$). In contrast, the associations were not statistically significant for chronic respiratory disease ($P = 0.065$) or multimorbidity ($P = 0.103$). However, the findings for conditions with small numbers of cases, particularly chronic respiratory disease, should be interpreted cautiously because sparse cell counts may affect the stability and reliability of the estimates (Table 4 and Figure 2).

**Table 2. Baseline demographic and clinical characteristics of the study population**

| Variable | Total n (%) or mean +/- SD | Male (n=104) | Female (n=118) | P-value |
|---|---|---|---|---|
| Age, years | 52.8 +/- 23.4 | 51.0 +/- 24.6 | 54.3 +/- 22.2 | 0.302 |
| Pediatric group (<18 years) | 19 (8.6) | 13 (12.5) | 6 (5.1) | 0.14 |
| Adults (18-59 years) | 101 (45.5) | 46 (44.2) | 55 (46.6) | 0.14 |
| Elderly (>=60 years) | 102 (45.9) | 45 (43.3) | 57 (48.3) | 0.14 |
| No recorded chronic disease | 8 (3.6) | 2 (1.9) | 6 (5.1) | 0.288 |
| Diabetes mellitus | 203 (91.4) | 98 (94.2) | 105 (89.0) | 0.163 |
| Documented heart failure | 182 (82.0) | 87 (83.7) | 95 (80.5) | 0.543 |
| Bronchial asthma | 52 (23.4) | 24 (23.1) | 28 (23.7) | 0.909 |
| Chronic respiratory disease | 6 (2.7) | 4 (3.8) | 2 (1.7) | 0.422 |

*P-values compare male and female patients. Age was assessed as a continuous variable, while categorical variables were assessed using chi-square or Fisher's exact test where appropriate.*

**Table 3. SARI symptom phenotype by age and sex**

| Symptom phenotype | Total n (%) | Age mean +/- SD | Age median (IQR) | Female n (%) | Male n (%) |
|---|---|---|---|---|---|
| Cough and fever | 199 (89.6) | 53.1 +/- 23.2 | 57 (37-70) | 103 (51.8) | 96 (48.2) |
| Fever only | 21 (9.5) | 50.5 +/- 24.9 | 53 (36-71) | 14 (66.7) | 7 (33.3) |
| Cough only | 2 (0.9) | 46.5 +/- 43.1 | 46 (31-62) | 1 (50.0) | 1 (50.0) |

*Age difference across symptom phenotypes: Kruskal-Wallis p=0.922. Sex distribution across symptom phenotypes: chi-square p=0.427.*

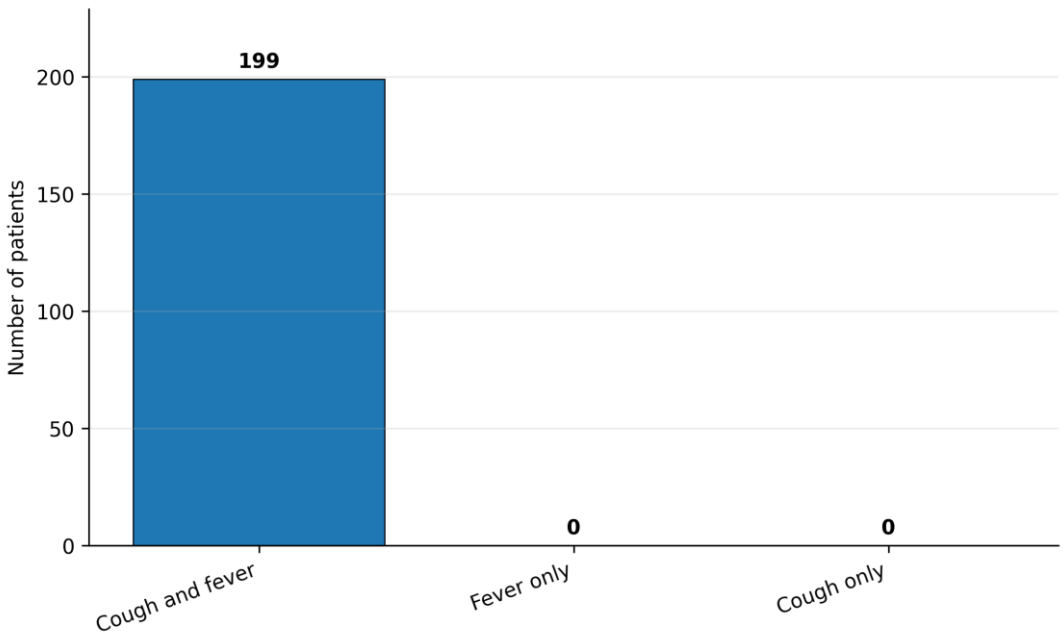


*Figure 1. Distribution of SARI symptom phenotypes. The bar chart shows the number of patients in each symptom category. Cough and fever were the dominant phenotype, supporting its use as the main complete SARI-compatible endpoint in subsequent analyses.*

**Table 4. Cross-tabulation of standardized chronic disease indicators by SARI symptom phenotype**

| Chronic disease variable | Fever only, n (%) | Cough only, n (%) | Cough and fever, n (%) | *P*-value |
|---|---|---|---|---|
| **No recorded chronic disease** | 3 (37.5) | 0 (0.0) | 5 (62.5) | 0.039* |
| **Diabetes mellitus** | 17 (8.4) | 1 (0.5) | 185 (91.1) | 0.023* |
| **Documented heart failure** | 13 (7.1) | 1 (0.5) | 168 (92.3) | 0.015* |
| **Bronchial asthma** | 12 (23.1) | 1 (1.9) | 39 (75.0) | <0.001* |
| **Chronic respiratory disease** | 0 (0.0) | 1 (16.7) | 5 (83.3) | 0.065 |
| **Multimorbidity (≥2 diseases)** | 16 (8.4) | 1 (0.5) | 173 (91.1) | 0.103 |

*Values are presented as numbers (row percentage). An asterisk indicates statistical significance at* P < *0.05.*

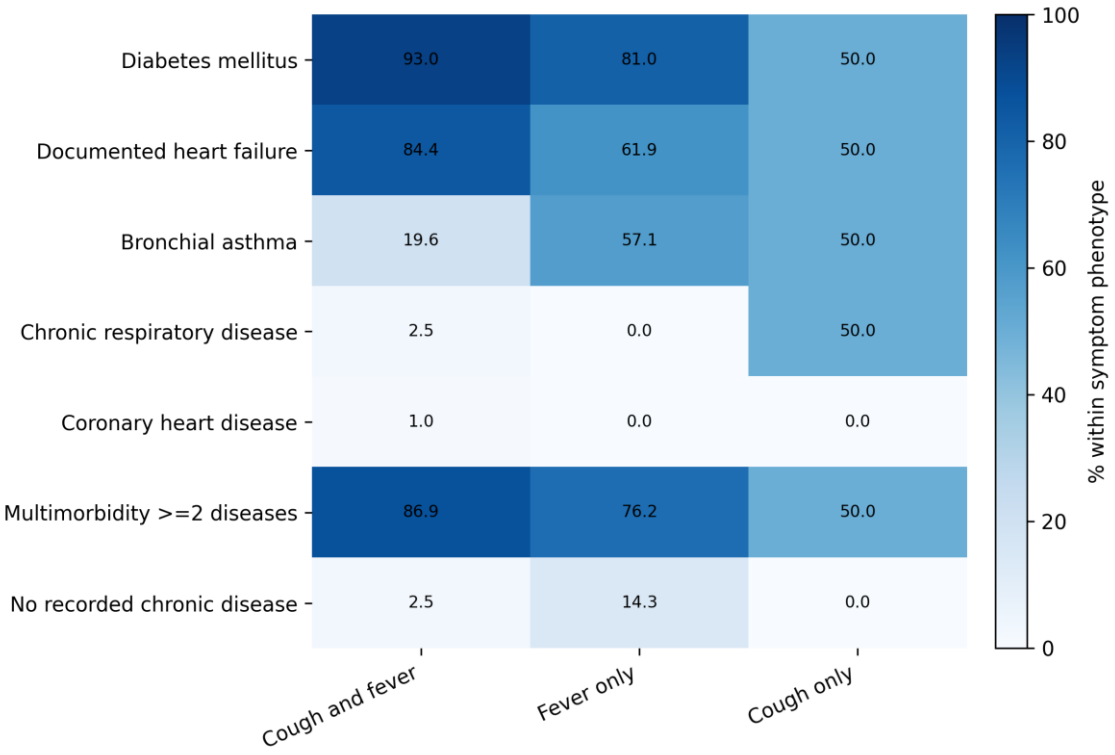


*Figure 2. Heatmap of chronic disease frequency within each SARI symptom phenotype. The heatmap provides a visual form of Table 4 by showing the percentage distribution of each chronic disease indicator across cough-and-fever, fever-only, and cough-only phenotypes. Darker shading indicates higher frequency within the symptom phenotype.*

### 3.4 Comorbidity-overlap structure and multimorbidity burden

The standardized comorbidity-overlap categories in Table 5 are also expressed with visuals in Figure 3. The prevalent comorbidity was diabetes mellitus with documented heart failure, which was evident in 142 individuals (64.0%). The next comorbidity pattern was the presence of diabetes mellitus, documented heart failure, and bronchial asthma, which was evident in 33 individuals (14.9%). Diabetes mellitus in the absence of other conditions was recorded in 14 individuals (6.3%). Absence of recorded chronic disease and bronchial asthma was noted in a few individuals. The patterns that were grouped as rare or complex multimorbidity were the less frequent combinations, which included chronic respiratory disease or coronary heart disease.

Figure 3 represents the comorbidity-overlap table diagrammatically. The upper bars display the frequencies of the various overlaps; the connected dots specify which chronic diseases belong to those patterns. This shows that the dataset was mostly made up of states with cardiometabolic overlaps and not with isolated respiratory comorbidity. Bronchial asthma was mostly noted as an added respiratory component to diabetes mellitus and documented heart failure, and not as a main isolated factor.

### 3.5 Logistic regression analysis of predictors of complete SARI symptom phenotype

Figure 3 represents the comorbidity-overlap table diagrammatically. The upper bars display the frequencies of the various overlaps; the connected dots specify which chronic diseases belong to those patterns. This shows that the dataset was mostly made up of states with cardiometabolic overlaps and not with isolated respiratory comorbidity. Bronchial asthma was mostly noted as an added respiratory component to diabetes mellitus and documented heart failure, and not as a main isolated factor.

The forest plot in Figure 4 shows the results from an adjusted logistic regression. The dashed vertical line shows the null value of OR=1. Predictors with confidence intervals that cross this line were interpreted as not statistically significant. After the adjustment, only bronchial asthma remained significant. The other variables (age, male sex, DM, documented heart failure, and multimorbidity) did not show statistically significant independent associations with the cough-and-fever phenotype.

### 3.6 Correlation between age, comorbidity burden, and SARI phenotype

The correlation analysis revealed that age positively correlated with greater numbers of comorbidities. This finding supports the assumption that chronic diseases increase with age. On the other hand, greater age was found to have no relationship with the cough-and-fever phenotype. This suggests that in the dataset, the symptom completeness of the cough-and-fever phenotype was more related to the disease itself and how it was presented clinically, rather than being related to age (Table 7).

**Table 5. Comorbidity-overlap structure using standardized manuscript labels**

| Comorbidity-overlap category | Diabetes mellitus | Documented heart failure | Bronchial asthma | Chronic respiratory disease | Coronary heart disease | Frequency n (%) |
|---|---|---|---|---|---|---|
| Diabetes mellitus + documented heart failure | Present | Present | Absent | Absent | Absent | 142 (64.0) |
| Diabetes mellitus + documented heart failure + bronchial asthma | Present | Present | Present | Absent | Absent | 33 (14.9) |
| Diabetes mellitus only | Present | Absent | Absent | Absent | Absent | 14 (6.3) |
| Bronchial asthma only | Absent | Absent | Present | Absent | Absent | 8 (3.6) |
| No recorded chronic disease | Absent | Absent | Absent | Absent | Absent | 8 (3.6) |
| Diabetes mellitus + bronchial asthma | Present | Absent | Present | Absent | Absent | 7 (3.2) |
| Other rare or complex comorbidity patterns | Variable | Variable | Variable | Variable | Variable | 10 (4.5) |

*Percentages were calculated from 222 paired records. Other rare or complex comorbidity patterns include uncommon combinations involving documented heart failure alone, diabetes with chronic respiratory disease, documented heart failure with bronchial asthma, and combinations involving CRD or CHD.*

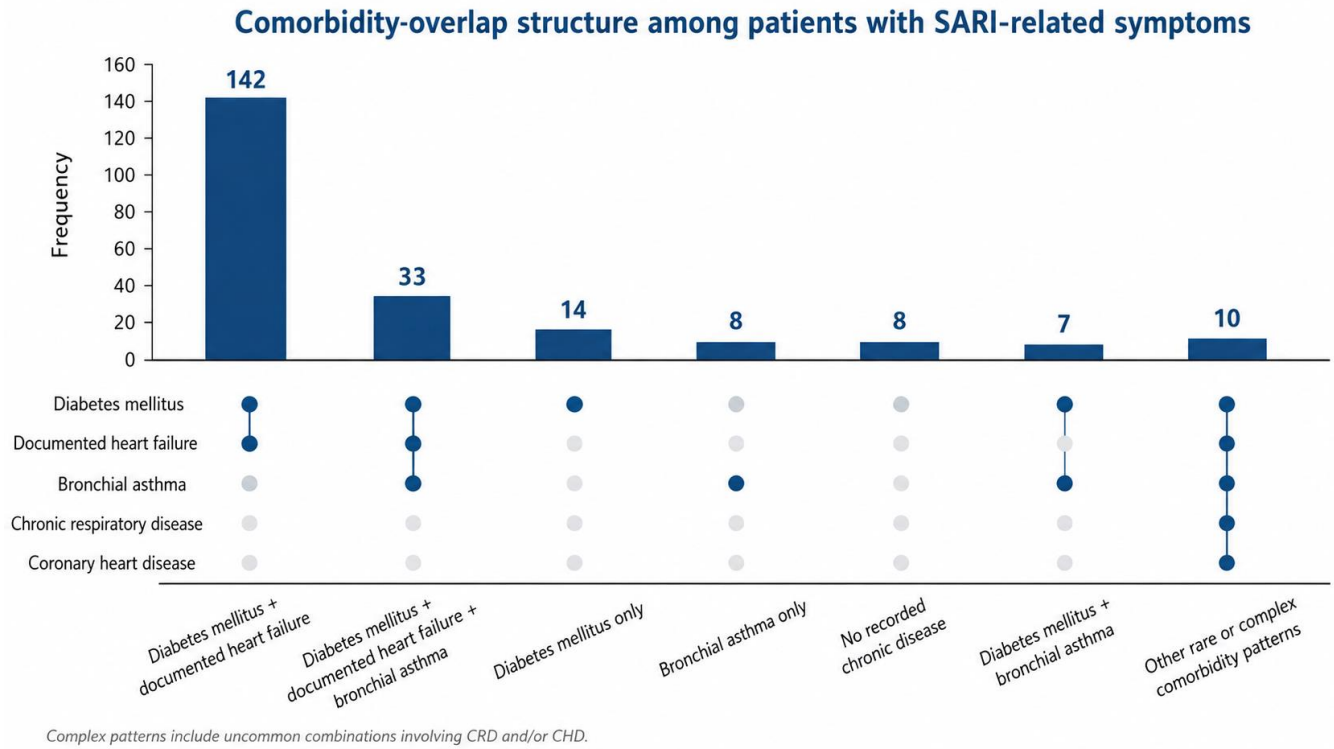


Figure 3. Comorbidity-overlap structure among patients with SARI-related symptoms. The upper bars represent the frequency of each standardized chronic disease combination, while the connected dots indicate the chronic diseases included in each overlap category. Diabetes mellitus with documented heart failure was the dominant pattern, followed by diabetes mellitus, documented heart failure, and bronchial asthma. Rare combinations involving chronic respiratory disease or coronary heart disease were grouped as complex multimorbidity patterns.

**Table 6. Logistic regression model for predictors of cough-and-fever SARI phenotype**

| Predictor | Crude OR | 95% CI | Adjusted OR | 95% CI | P-value |
|---|---|---|---|---|---|
| Age | 1.01 | 0.99-1.02 | 1.0 | 0.98-1.03 | 0.752 |
| Male sex | 1.75 | 0.71-4.31 | 1.71 | 0.66-4.46 | 0.273 |
| Diabetes mellitus | 3.67 | 1.19-11.36 | 1.52 | 0.18-12.80 | 0.702 |
| Documented heart failure | 3.48 | 1.39-8.75 | 2.53 | 0.55-11.67 | 0.233 |
| Bronchial asthma | 0.19 | 0.08-0.46 | 0.22 | 0.08-0.62 | 0.004* |
| Multimorbidity >=2 diseases | 2.35 | 0.85-6.50 | 0.71 | 0.06-7.91 | 0.781 |

*The adjusted model included age, sex, diabetes mellitus, documented heart failure, bronchial asthma, and multimorbidity >=2 diseases. OR, odds ratio; CI, confidence interval.*

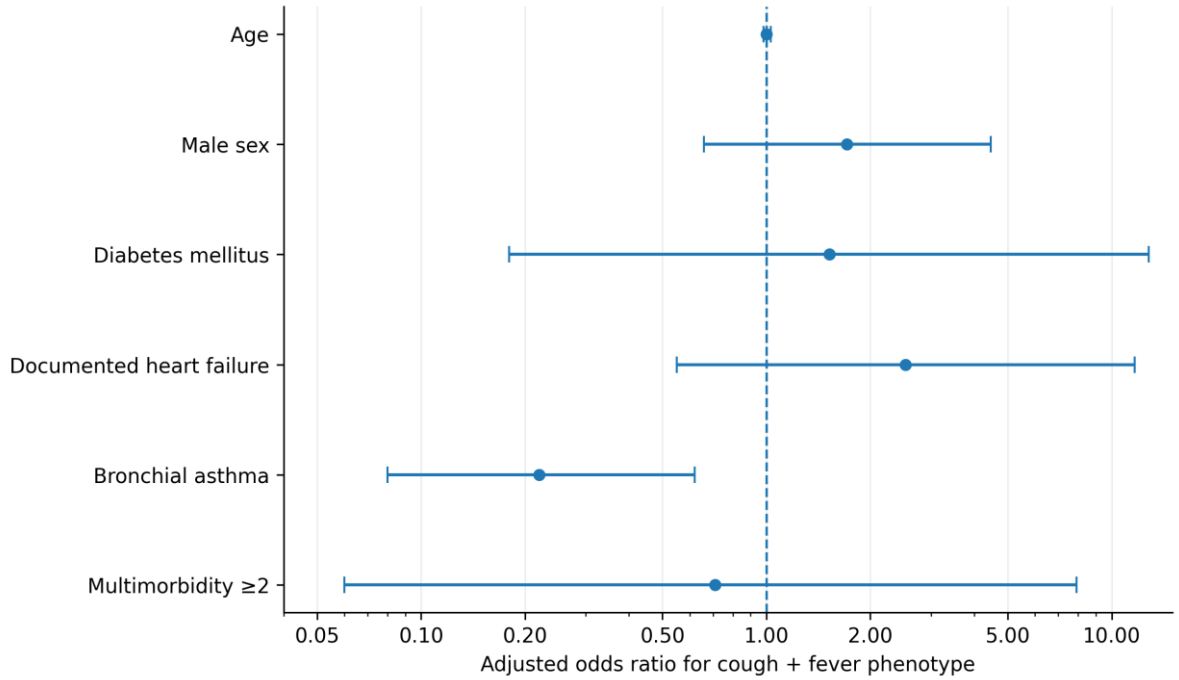


*Figure 4. Adjusted predictors of cough-and-fever SARI phenotype. The forest plot shows adjusted odds ratios and 95% confidence intervals for predictors of the complete SARI phenotype. The dashed vertical line represents OR=1. Confidence intervals crossing this line indicate non-significant associations. Bronchial asthma showed a significant inverse association after adjustment.*

**Table 7. Correlation summary for age, comorbidity burden, and complete SARI phenotype**

| Relationship | Statistic | P-value | Interpretation |
|---|---|---|---|
| Age vs comorbidity count | Spearman rho = 0.304 | <0.001 | Increasing age was associated with greater chronic disease burden. |
| Age vs cough-and-fever phenotype | Spearman rho = 0.027 | 0.692 | Age was not meaningfully associated with the cough-and-fever phenotype. |

## 4. Discussion

This study examines a SARI-related database of clinical cases with dominant cough and fever and a high burden of chronic cardiometabolic disease. The most noteworthy finding was that cough-and-fever presentations constituted almost 90% of the case records. This finding is significant since cough-and-fever presentations are critical to the definition of case reporting and surveillance of SARI, and indicate the involvement of a respiratory system case and a systemic inflammatory response [1].

The other significant finding was the presence of diabetes and heart failure, especially as a combined pattern of comorbidity. This finding indicates that, within the context of the dataset, SARI-related cases are likely to occur among the population with diabetes and heart failure, and most likely, diabetes. Diabetes, in particular, is associated with impaired host defense and with impairment of the function of leukocytes and of the diabetic inflammatory response, as well as heart failure [3,4]. Documented heart failure may reduce the support of the cardiopulmonary system and increase the possible clinical effects of an acute respiratory illness, in particular, complicated illness with fever and symptoms of a respiratory nature that increase oxygen demand [5].

The overlap of comorbidities was significant, namely, that the dataset was poorly characterized by an enumeration of the individual chronic conditions. Most patients had multiple chronic conditions, the most frequent overlap being diabetes and heart failure. This observation was consistent with the conclusion by the authors that the presence of multiple chronic conditions was of clinical significance and not of statistical significance. The most recent studies of respiratory viral illness also provide evidence to support the presence of cardiovascular, respiratory, and metabolic comorbidities as overlapping risk factors for severe respiratory illness [3,8].

Bronchial asthma exhibited a particular behavior. In adjusted logistic regression analysis, asthma showed a negative association with the cough-and-fever phenotype. This should not be interpreted as evidence of decreased risk of respiratory infection [11]. It may be an indication of another way of expressing symptoms. In the case of asthma, the expression may be of airway hyperreactivity and cough, appearing even in the absence of a systemic fever. Asthma may be a good example of the condition of cough and fever, as hyperreactive airway epithelium may respond differentially to the same viral infection. The inverse adjusted association may be interpreted as a change of phenotype, rather than a decrease of clinical risk [12].

Age is associated with comorbidity burden, but not with cough-and-fever phenotype. The absence of the cough-and-fever phenotype may be due to the accumulating chronic inflammatory diseases with age, as the expression of cough and fever may depend on the pathogen, host response, medications, and timing of clinical presentation [13-15].

Therefore, it is appropriate to say that age may be a modifier in a background situation of multimorbidity, while other chronic diseases act as the primary drivers of cough-and-fever symptoms.

This study contains a few limitations. The analyses were performed on paired records based on data blocks. Therefore, the workflow should be repeated on the original Excel documents, prior to submission to the journal, to verify the alignment of records. Some of the subgroups, including cough-only phenotype, chronic respiratory conditions, and coronary heart disease, had small sample sizes, which limited statistical precision and resulted in wider confidence intervals. There was also no information on pathogen testing, oxygen saturation, outcome of hospitalization, medication history, vaccination status, and laboratory inflammatory markers. Nonetheless, the dataset aids in establishing a comprehensive and analytical

framework on the association of chronic disease and SARI symptom phenotypes.

## 5. Conclusion

The analyzed records showed that dominant cough and fever-related symptoms of acute respiratory illness (SARI) were associated with a significant burden of cardiometabolic comorbidity, including diabetes combined with registered heart failure and bronchial asthma in a small group as an additional respiratory component. Multimorbidity analysis was more informative than isolated counts of individual diseases. This indicates that in patients with SARI-related symptoms, clinical and epidemiological evaluations should include the chronic disease overlap and comorbidity burden.

Cohort Summary: A dominant presentation among the studied records was a cough-and-fever-related SARI presentation. There was a significant burden of cardiometabolic comorbidities. The hallmark of the cohort was multimorbidity, and more specifically, diabetes mellitus associated with documented heart failure. These findings support the benefits of assessing the overlap of different chronic conditions rather than assessing chronic conditions in isolation among patients who present with SARI-related symptoms.

## Data availability and ethics statement

This manuscript was prepared using anonymized, de-identified tabulated clinical data provided for analytical writing and visualization. No personal identifiers were included in the analysis. The final analysis should be verified against the original Excel dataset before formal submission.

**Conflict of interest:** NIL

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