

Lower respiratory tract infection in the community: associations between viral aetiology and illness course

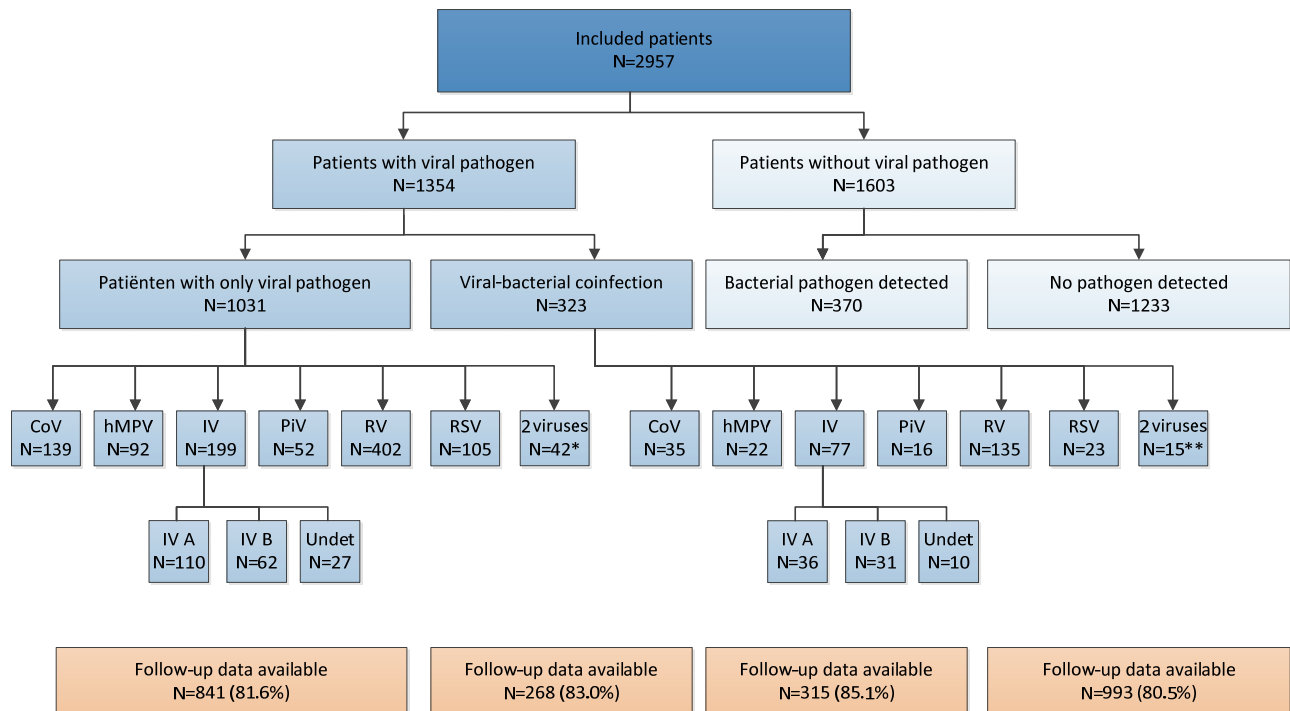
Peer-reviewed author version

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**Figure 1.** Detected viral pathogens in included patients (n=2957) and availability of follow-up data.

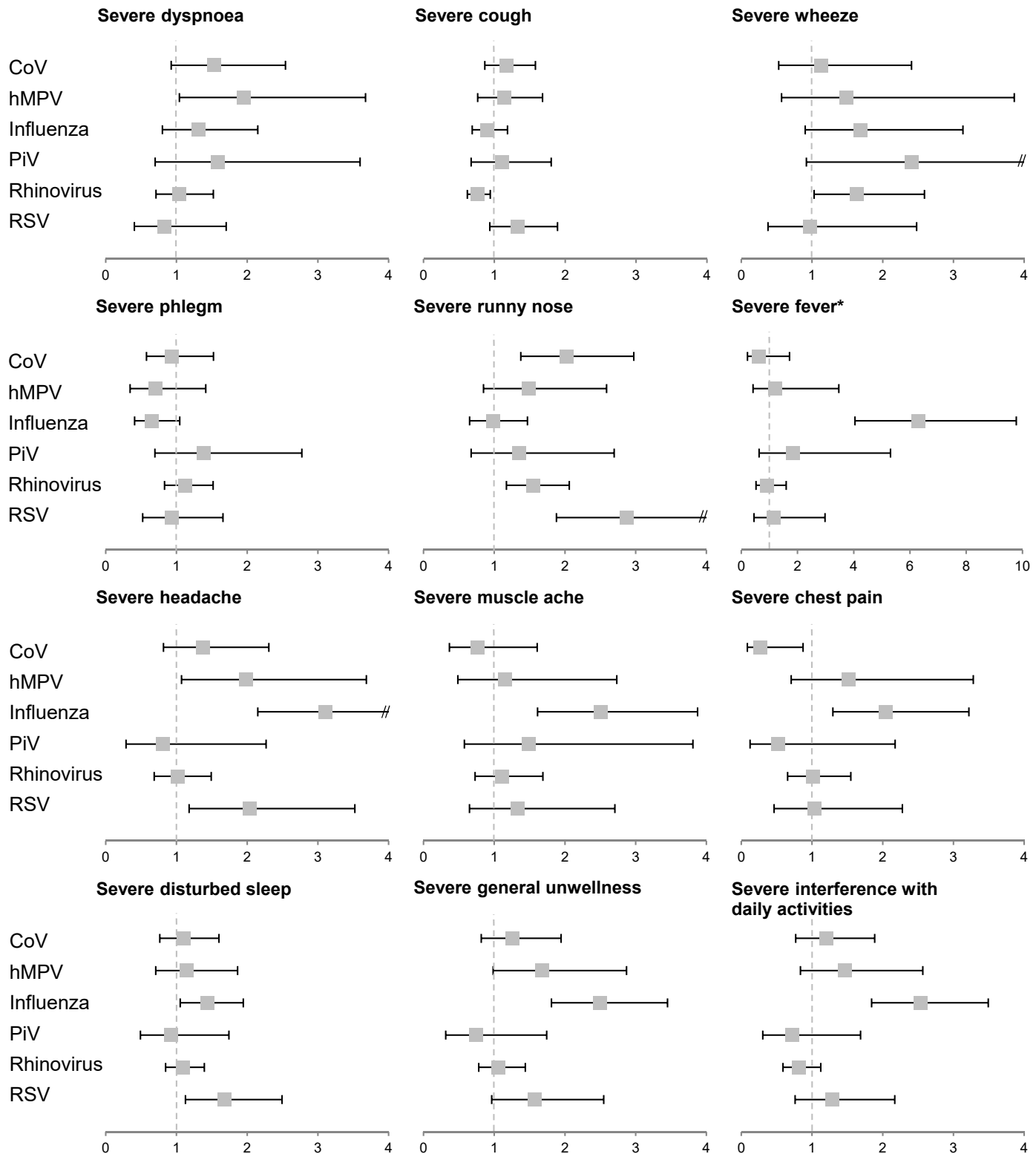


CoV, coronavirus; hMPV, human metapneumovirus; IV, influenza virus; PiV, Parainfluenza virus; RV, rhinovirus; RSV, respiratory syncytial virus; Undet, influenza virus type undetermined.

\* The following combinations of viral pathogens were found: CoV + RV (n=10), IV + RV (n=8), CoV + hMPV (n=5), CoV + RSV (n=4), RV + RSV (n=4), IV + RSV (n=3), CoV + IV (n=2), hMPV + RV (n=2), IV + PiV (n=1), CoV + PiV (n=1), RV + PiV (n=1), RSV + PiV (n=1).

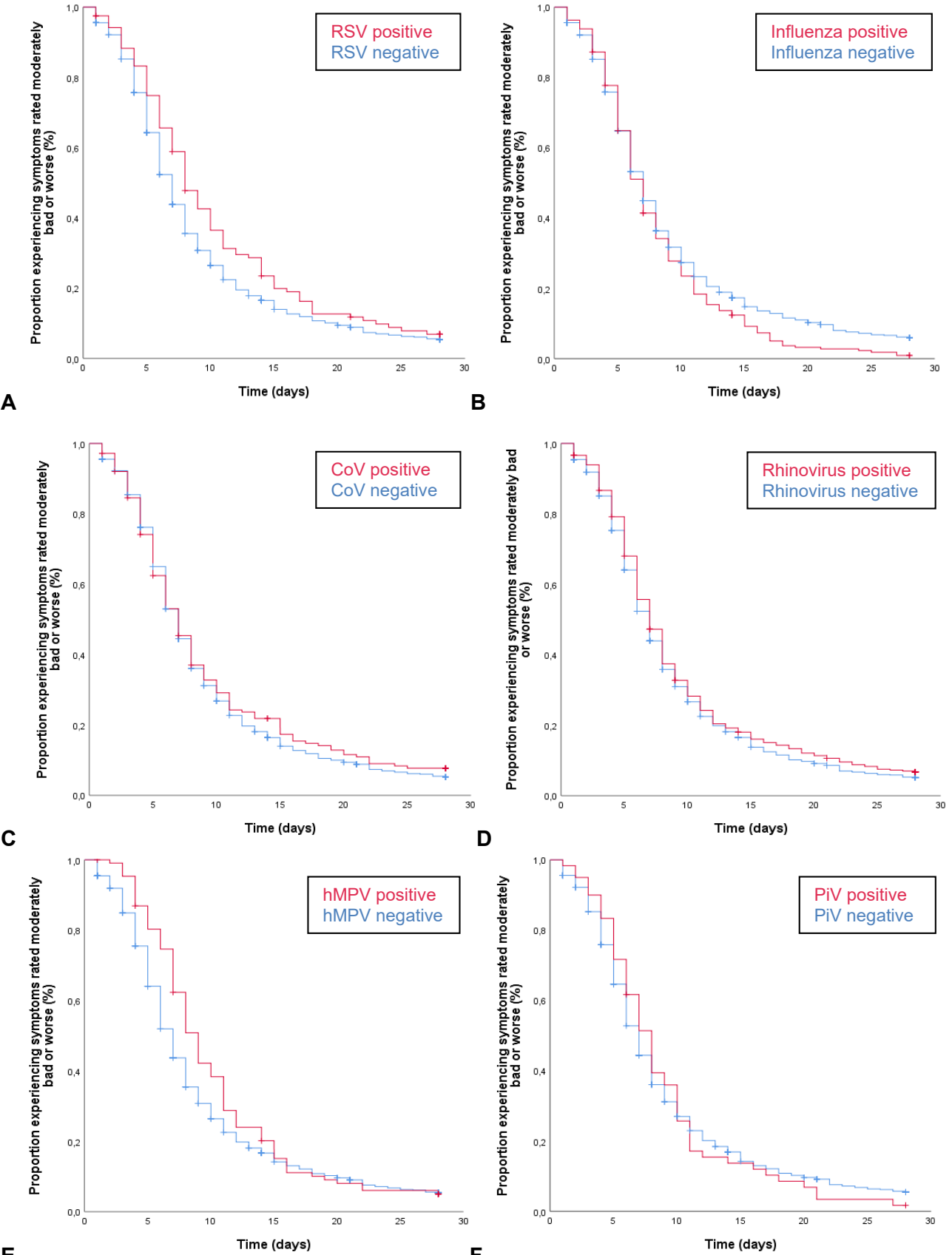
\*\* The following combinations of viral pathogens were found: CoV + RV (n=5), IV + RV (n=3), CoV + IV (n=3), CoV + RSV (n=1), RV + RSV (n=1), IV + RSV (n=1), RV + PiV (n=1).

**Figure 2.** Forest plots showing odds ratios (with 95%CI) for CoV, hMPV, influenza virus, PiV, rhinovirus and RSV for a severe burden of individual symptoms at presentation (highest on 4-point Likert scale). Odds ratios are derived from logistic multivariate regression models with adjustment for bacterial and viral coinfections, age, gender, pulmonary comorbidities (asthma, COPD and other lung diseases), hearth failure, current smoking, influenza vaccination during the preceding fall or winter, and duration of symptoms before presentation.

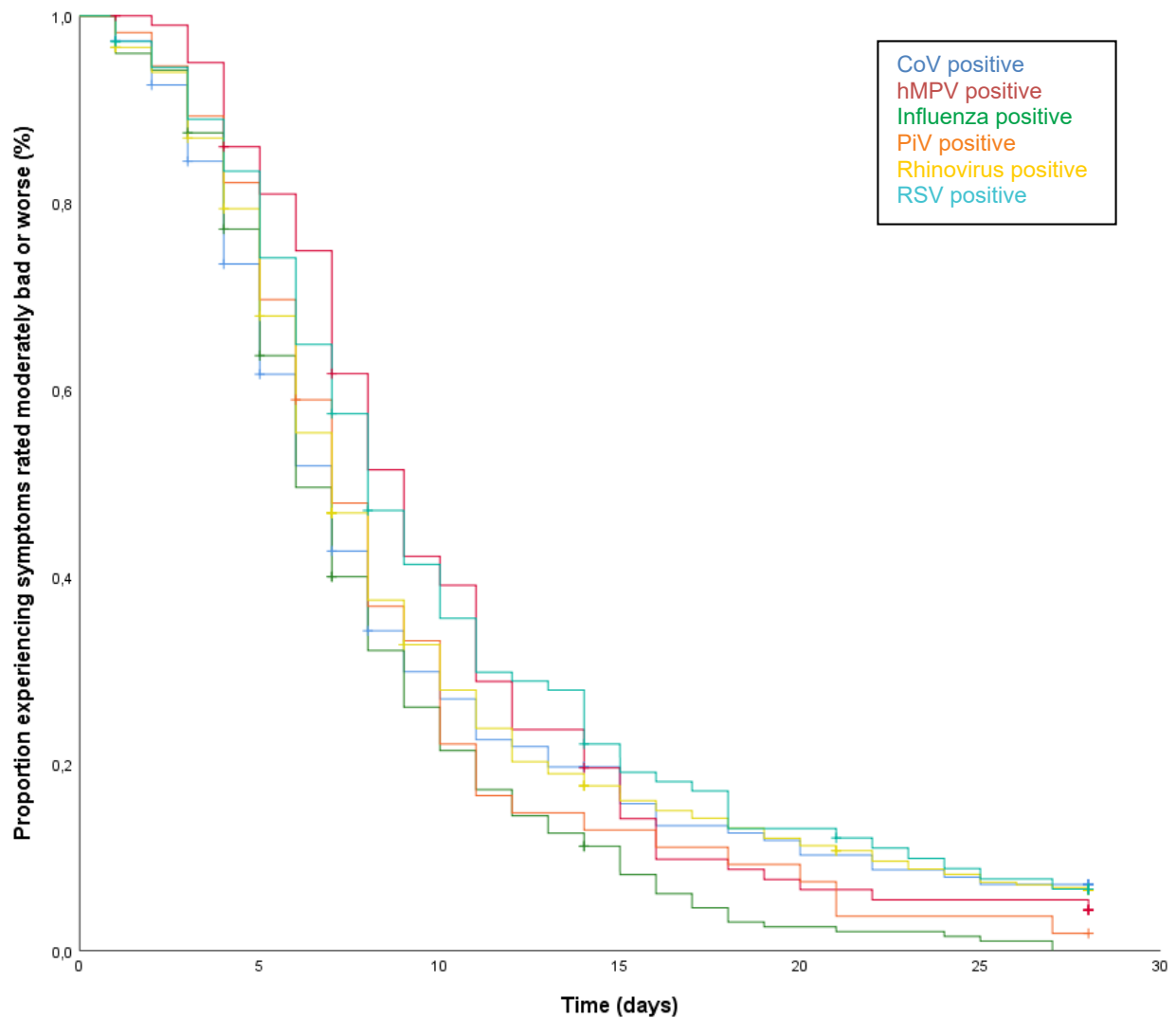


\* For fever the scale on the x-axis was altered for visual purposes.

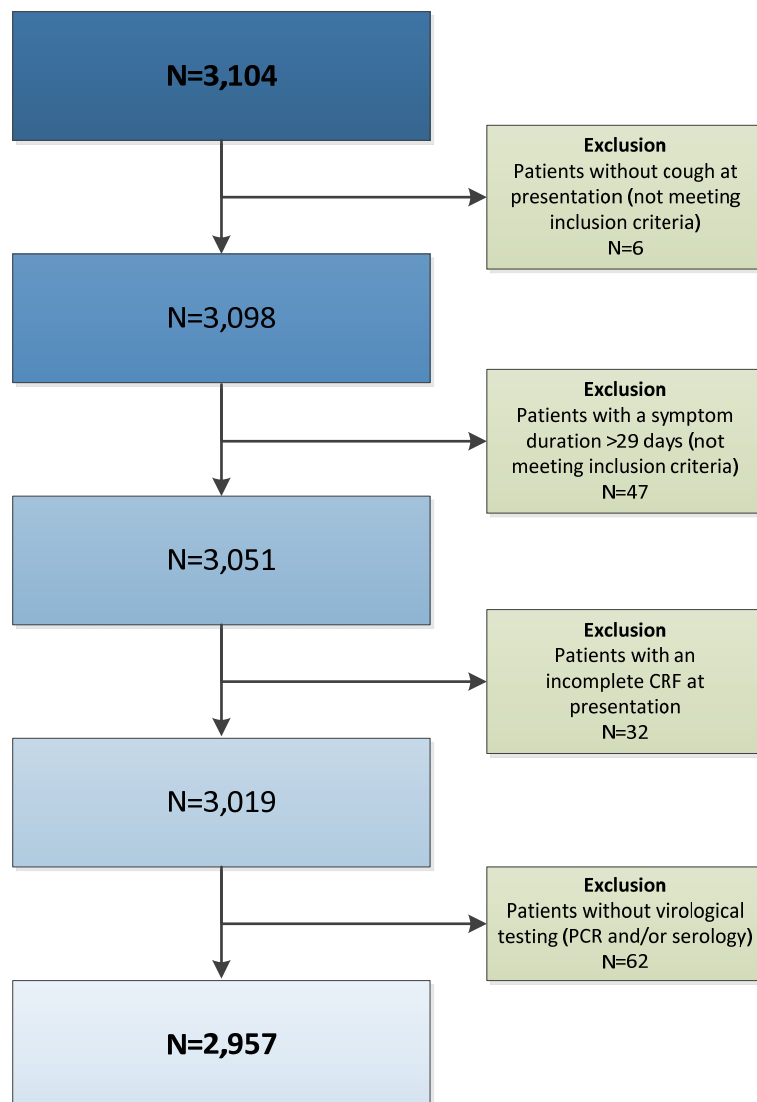
**Figure 3.** Kaplan-Meier survival curves for the duration of symptoms rated moderately bad or worse in patients with LRTI (n=2393), stratified by A) RSV positive or negative, B) influenza virus positive or negative, C) CoV positive or negative, D) rhinovirus positive or negative, E) hMPV positive or negative and F) PiV positive or negative.



**Figure 4.** Kaplan-Meier survival curve for the duration of symptoms rated moderately bad or worse in patients with LRTI and a viral mono infection (n=1056), stratified by viral aetiology (note: patients with viral coinfections were excluded).



**Supplementary Figure 1.** Flow-chart patient exclusion as compared to the total number of patients included in the GRACE cohort(1).



**Table 1.** *Baseline characteristics included patients (n=2957).*

<b>Demographics</b>	<b>Patients (n=2957)<sup>a</sup></b>
Age (years)	50 (36-63)
Gender (male)	1195 (40.4%)
Caucasian ethnicity	2862 (96.8%)
Comorbidities <sup>b</sup>	
COPD	176 (6.0%)
Asthma	307 (10.4%)
Other lung disease	62 (2.1%)
Heart failure	57 (1.9%)
Ischemic heart disease	159 (5.4%)
Other hearth disease	111 (3.8%)
Diabetes	190 (6.4%)
Smoking past or current	1603 (54.2%)
<b>Disease related characteristics at presentation</b>	
Severe cough	983 (33.2%)
Sputum production	309 (10.4%)
Shortness of breath	215 (7.3%)
Wheeze	115 (3.9%)
Blocked or runny nose	355 (12.0%)
Fever	122 (4.1%)
Chest pain	155 (5.2%)
Muscle aching	163 (5.5%)
Headache	226 (7.6%)
Disturbed sleep	542 (18.3%)
Feeling generally unwell	349 (11.8%)
Interference with normal daily activities	344 (11.6%)
Confusion/disorientation	6 (0.2%)
Diarrhoea	16 (0.5%)
One or more abnormalities at lung auscultation	1165 (39.4%)
Breaths (per minute)	16 (15-18)
Heart rate (beats per minute)	76 (70-83)
Systolic blood pressure (mmHg)	127 (117-140)
Diastolic blood pressure (mmHg)	80 (70-85)
Oral temperature (degrees Celsius)	36.7 (36.4-37)
Medication prescribed for illness <sup>c</sup>	2086 (70.5%)

<sup>a</sup> Demographics are given as absolute numbers with % for categorical variables or as median with interquartile range (IQR) for continuous variables. <sup>b</sup> Some patients had multiple comorbidities. <sup>c</sup> Prescribed medication included antibiotics, antitussives, mucolytic drugs, antihistamines, bronchodilators and anti-inflammatory drugs.

**Table 2.** Symptom severity<sup>a</sup> at presentation in patients consulting in primary care with a detected virus or no detected virus (n=2957).

	Mean (SD) symptom score at presentation	Difference for subgroup (95% CI) <sup>b</sup>	p-value
<b>No virus(es)</b> (n=1603)	2.02 (0.49)	-	-
<b>≥1 virus(es)</b> (n=1354)	2.18 (0.52)	0.13 (0.10-0.17)	<.001
<b>1 virus</b> (n=1297)	2.18 (0.51)	0.13 (0.09-0.16)	<.001
<b>2 viruses</b> (n=57)	2.27 (0.54)	0.22 (0.09-0.35)	0.001
<b>CoV</b> (n=205)	2.15 (0.48)	0.09 (0.02-0.16) <sup>c</sup>	0.011
<b>hMPV</b> (n=121)	2.18 (0.52)	0.16 (0.07-0.26) <sup>c</sup>	<.001
<b>Influenza virus</b> (n=297)	2.32 (0.55)	0.25 (0.19-0.31) <sup>c</sup>	<.001
<b>PiV</b> (n=73)	2.13 (0.51)	0.07 (-0.04-0.19) <sup>c</sup>	0.214
<b>Rhinovirus</b> (n=572)	2.15 (0.50)	0.07 (0.02-0.12) <sup>c</sup>	0.003
<b>RSV</b> (n=143)	2.17 (0.53)	0.12 (0.04-0.21) <sup>c</sup>	0.004

<sup>a</sup> Calculated as the mean (standard deviation) symptom severity score for all 12 symptoms at presentation.

<sup>b</sup> Estimates controlled for age, gender, pulmonary comorbidities (asthma, COPD and other lung diseases), hearth failure, current smoking, influenza vaccination during the preceding fall or winter, coinfection with at least one respiratory bacterium or with Aspergillus and duration of symptoms before presentation.

<sup>c</sup> Estimates additionally controlled for coinfection with another respiratory virus.



**Table 3.** Symptom duration<sup>a</sup> (days) in patients consulting in primary care with detected virus or no detected virus (n=2393). A hazard ratio <1 indicates a disadvantageous effect on symptom resolution.

	Median (IQR) time to resolution of symptoms rated moderately bad or worse	Hazard ratio for subgroup (95% CI) <sup>b</sup>	p-value
<b>No virus(es)</b> (n=1288)	6 (4-10)	-	-
<b>≥1 of six viruses</b> (n=1105)	7 (5-11)	0.97 (0.89-1.06)	0.479
<b>1 of six viruses</b> (n=1056)	7 (5-11)	0.98 (0.89-1.07)	0.580
<b>2 of six viruses</b> (n=49)	8 (5-15)	0.89 (0.66-1.21)	0.456
<b>CoV</b> (n=177)	7 (4-11)	0.97 (0.82-1.15) <sup>c</sup>	0.751
<b>hMPV</b> (n=108)	8 (6-12)	0.81 (0.66-1.00) <sup>c</sup>	0.052
<b>Influenza</b> (n=243)	7 (5-10)	1.20 (1.04-1.39) <sup>c</sup>	0.013
<b>PiV</b> (n=60)	8 (5-11)	0.94 (0.72-1.23) <sup>c</sup>	0.649
<b>Rhinovirus</b> (n=445)	7 (5-11)	0.94 (0.84-1.05) <sup>c</sup>	0.291
<b>RSV</b> (n=121)	8 (5-14)	0.82 (0.67-1.00) <sup>c</sup>	0.048

<sup>a</sup> Calculated as the median (IQR) number of days with symptoms rated moderately bad or worse by the patient following initial presentation.

<sup>b</sup> Estimates controlled for age, gender, pulmonary comorbidities (asthma, COPD and other lung diseases), hearth failure, current smoking, influenza vaccination during the preceding fall or winter, coinfection with at least one respiratory bacterium or with Aspergillus, duration of symptoms before presentation and baseline symptom severity (12-symptom score).

<sup>c</sup> Estimates additionally controlled for coinfection with another respiratory virus.