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Summary

Introduction: SARS-CoV-2 dramatically revealed the sudden impact of respiratory viruses in our lives. Influenza and respiratory syncytial virus (RSV) infections are associated with high rates of morbidity, mortality, and an important burden on healthcare systems worldwide, especially in elderly patients. The aim of this study was to identify severity predictors in the oldest-old admitted with Influenza and/or RSV infections.

Methods: This is a multicentre, retrospective study of all oldest old patients (≥ 85 years-old) admitted for laboratory-confirmed Influenza and/or RSV infection in three tertiary hospitals in Portugal, Italy, and Cyprus over two consecutive winter seasons. The outcomes included the following: pneumonia on infection presentation, use of non-invasive ventilation (NIV), and in-hospital death (IHD). The association with possible predictors, including clinical features and type of virus infection, was assessed using uni- and multivariable analyses.

Results: 251 oldest old patients were included in the study. Pneumonia was evident in 32.3% (n=81). NIV was implemented in 8.8% (n=22) and IHD occurred in 13.9% (n=35). Multivariable analyses revealed that chronic obstructive pulmonary disease (COPD) or asthma was associated with pneumonia (OR 1.86; 95% CI 1.02-3.43; p=0.045). COPD or asthma (OR 4.4; 95% CI 1.67-11.6; p=0.003), RSV (OR 3.12; 95% CI 1.09-8.92; p=0.023) and Influenza-B infections (OR 3.77; 95% CI 1.06-13.5; p=0.041) were associated with NIV use, respectively, while chronic kidney disease was associated with IHD (OR 2.50; 95% CI 1.14-5.51; p=0.023).

Discussion: Among the oldest-old, chronic organ failure such as COPD or asthma and CKD predicted pneumonia and IHD, respectively, beyond the importance of viral virulence itself. These findings could impact on public health policies such as fostering Influenza immunization campaigns, home-based care programmes and end-of-life care. Filling knowledge gaps is crucial to set priorities and advise on transition model of care that best fits the oldest-old.

Keywords: oldest-old; influenza; respiratory syncytial virus; geriatrics; pneumonia

Introduction

SARS-CoV-2 dramatically revealed the sudden impact and the utmost importance of respiratory viruses in our lives. Influenza and respiratory syncytial virus (RSV) infections are associated with high rate of morbidity, mortality, and an important burden on healthcare systems worldwide, especially among elderly patients [1-6]. Oldest-old is a term meant to include people aged 85 years and older that represent a growing population in the old European continent. Despite being a non-homogeneous group, they are professionally retired individuals that usually experience multimorbidity, disability and may face a limited life expectancy. Recent evidence suggests that there is a high research interest towards addressing their needs and establishing the best standard of care [7,8]. Especially in epidemiological research, oldest old patients are considered to be a part of the wider age group of the elderly (≥65 years-old) and there is limited published evidence about predictors of severity of illness and mortality in viral infections, such as caused by Influenza and RSV. The aim of this study was to describe the clinical features of an oldest old population admitted with Influenza and/or RSV infections in three southern European hospitals over two consecutive winter seasons and identify predictors of pneumonia, non-invasive ventilation (NIV) and in-hospital death (IHD). Such knowledge might provide insight to assist healthcare policymakers managing chronic conditions, improving patient satisfaction and reduce hospital utilization.

Methods

This is a multicentre, retrospective study of all oldest old patients (≥85 years-old) who were either admitted to the hospital for laboratory-confirmed Influenza and/or RSV infection or developed it during the course of admission for other causes, from 1 October 2017 to 30 April 2018 and from 1 October 2018 to 30 April 2019 in three tertiary hospitals in Portugal, Italy and Cyprus. The laboratory confirmation was based on a positive Xpert Flu/RSV PCR (Cepheid Diagnostics, Sunnyvale, CA, USA) and/or Allplex Respiratory Panel (Allplex, Seegene, Republic of Korea) on naso/oropharyngeal swabs obtained from patients with signs or symptoms of viral infection. For patients with more than

one positive PCR in a seasonal period, the first episode was considered for study purposes. The infection was characterized as hospital-acquired if symptoms pertaining to viral infection began after 72 h from admission. Variables assessed included demographics, smoking status, co-morbidities, virus type, nosocomial acquisition, pulmonary infiltrate on chest x-ray taken when symptoms were observed, neuraminidase inhibitor use, length of stay (from admission to discharge), NIV, mechanical ventilation and IHD.

This study was conducted in accordance with the Declaration of Helsinki. Formal ethical approval was obtained by the institutional review board of the coordinating centre (Central Lisbon Hospital Centre, no. 762_2019). Informed consent was not deemed required for the purposes of this study.

Statistical analysis

Descriptive data are shown as absolute (n) and relative (%) frequencies for categorical data and as mean ± standard deviation (SD) and median and interquartile range (IQR), as appropriate, for continuous variables. On univariate analysis, chi-square test for categorical variables, and t-Student or Wilcoxon rank-sum test, as appropriate, for continuous variables were carried out to identify factors associated with pneumonia, NIV and IHD. Odds ratios (OR) and their 95%confidence intervals (95%CI) were also calculated to estimate the strenght of those associations. Multivariable analysis models were then fitted to investigate the independent effects of type of virus infection and clinically variables that turned out to be significantly associated with the outcomes at univariate analysis, adjusting for possible confounders like age and gender.

For all tests, a p-value ≤ 0.05 was considered significant.

All analyses were performed with Stata 14.

Results

A total of 1,151 patients ≥18 years-old were admitted for Influenza A/B and/or RSV infections during the study period in the three centres. Oldest old patients were 251 (21.8%), of which 30 (12%) had hospital-acquired Influenza A/B and/or RSV infections.

Clinical features of oldest old patients included in the study were reported in Table 1. Mean age was 89.4 ± 3.9 [range, 85 to 103] years, 79 (31.5%) were men and 3.6% was current active smoker. The co-morbidities mainly observed were diabetes (22.7%), COPD or asthma (24.7%), CHF (47%) and CKD (19.5%). The viral agents identified were Influenza-A (56.6%), Influenza-B (15.9%), RSV (25.9%), Influenza-A+Influenza-B (1.2%) and Influenza-A+RSV (0.4%) co-infections. Among Influenza-A infections, H3N2 was the most common (68.5%) followed by H1N1 (13%), 18.5% not having been subtyped. Radiological signs of pneumonia were present on the chest x-ray exams of 32.3% (n=81) following laboratory diagnosis of viral infection; 8.8% (n=22) were submitted to NIV and only one patient (0.4%) was invasively mechanically ventilated. Thirty-five patients (13.9%) did not survive admission. Among patients submitted to NIV, 72.7% (n=16) survived admission. Antiviral treatment with a neuraminidase inhibitor was started in 60.6% of patients. Mean length of stay of patients with community- and hospital-acquired infections was 12 ± 11.1 (median 9, IQR 6-14) and 27.8 ± 28.7 (median 20, IQR 8-30) days, respectively (p<0.01). Overall IHD was 13.9%, being 14% and 13.3% for community- and hospital-acquired infections, respectively, with no significant difference.

Results of univariate and multivariable analyses were shown in Table 2.

~~Since at univariate analysis FLU-A infection turned out to be a significant protective factor for NIV use (p=0.009)…~~

At univariate analysis, COPD or asthma were significantly associated with pneumonia (OR 1.93; 95% CI 1.06-3.49) and use of NIV (OR 3.49; 95% CI 1.43-8.51); RSV infection turned out to be another significant factor associated with NIV use (OR 3.51; 95% CI 1.27-9.68), while CKD was the only clinical feature significantly associated with IHD (OR 2.52; 95% CI 1.15-5.52). Finally, we considered three logistic regression models, where, for each outcome, age, gender, COPD or asthma

(for pneumonia and use of NIV models), CKD (for IHD model) and type of virus infection were the independent variables.

Among all patients, multivariable analyses revealed that COPD or asthma were significantly associated with radiologically confirmed pneumonia (OR 1.86; 95% CI 1.02-3.43; p=0.045); COPD or asthma (OR 4.4; 95% CI 1.67-11.6; p=0.003), Influenza-B (OR 3.77; 95% CI 1.06-13.5; p=0.041) and RSV infections (OR 3.12; 95% CI 1.09-8.92; p=0.023) were associated with NIV use; CKD turned out to be the only predictor significantly associated with IHD (OR 2.50; 95% CI 1.14-5.51; p=0.023).

Discussion

SARS-CoV-2 pandemia and its unsustainable burden supplanted every hierarchy of interest in medical research but highlighted how viral infections knowledge is crucial in clinical practice. Among the aged population, Influenza and RSV infections are important causes of hospital admission during autumn and winter months.

The highlights of this study are the following findings: (1) the proportion of oldest old patients among total hospitalizations was remarkable; (2) radiological pneumonia, use of NIV and IHD were considerable; (3) Influenza-A H3N2 infection was the most prevalent; Influenza-B and RSV infection were significantly associated with NIV use; (4) COPD or asthma was associated with both pneumonia and NIV use; (5) CKD was a predictor of IHD.

To best of our knowledge, our line of research is quite novel and barely comparable to previous reports given the higher mean age of patients involved.

Overall, the number of hospitalizations over the study period was remarkable comparing to recent reports [9], showing that over two years one out of five admissions with Influenza and/or RSV infections involved oldest-old. Moreover, in our study, hospital-acquired Influenza and/or RSV infections were not identified as predictors of pneumonia, use of NIV and IHD for patients aged 65 years and older, moving away from evidence available so far [9,10].

Pneumonia on infection presentation was very frequent, in line with more recent reports [9-17], revealing how an important proportion of patients showed a direct viral injury in lung parenchyma and/or bacterial co-infection. However, despite being a life-threatening condition it was neither predictive of NIV use nor of IHD.

The use of NIV was considerable when comparing with available evidence in a cohort of younger patients [9]. This finding might be related to both the type of respiratory failure on infection presentation and a remarkable rate of diagnosed or likely under-diagnosed chronic obstructive lung disease [18]. Similarly, in our population NIV seemed to be effective since data about its use in respiratory viral infections are limited and uncertain, especially in presence of pneumonia, hypoxemic respiratory failure, and SOFA≥5 and no COPD and/or cardiogenic pulmonary edema [19].

On the other hand, invasive mechanical ventilation rate was performed only once, probably according to ethical and prognostic considerations such as coexistence of frailty and patient end-of-life preferences. The discrepancy between the use of these two modalities of ventilation could be presumably due to accept NIV as a ceiling of therapeutic effort.

IHD was also remarkable. Studies suggest mortality rate ranging from 4.1% to 9.8% [9-13,15-17,20] and up to 24% in ICU patients [14]. Nevertheless, these studies were performed on elderly people with lower median age while our data should be comprehensible for an oldest old cohort of patients.

Infection due to Influenza-A H3N2 was the most prevalent, RSV infection was also very frequent, confirming that epidemic viral subtypes and their affinity for the lower respiratory tract differ according to the study period [21]. Severity of illness and IHD due to RSV infection were similar as compared to Influenza viruses but according to literature, these can vary from season to season [9,22].

Therefore, the role of virus type in morbidity and mortality remains controversial. ~~Our study set forth only a virus type association with NIV use.~~ Our findings might suggest that RSV and Influenza-B probably caused infections with a clinical scenario that benefited from application of NIV [23] more than Influenza-A.

COPD or asthma was independently associated with pneumonia on infection presentation and NIV use, suggesting the importance of the aged lung [18] and the attempt to overcome respiratory failure through this widespread and generally well-tolerated ventilation technique.

CKD was the only significant predictor IHD and it could represent an interesting clinical tool. Indeed, previous studies included acute kidney injury and renal disease as predictors of mortality and disease severity, respectively [9,12] but no prognostic factors have been identified for oldest-old.

Our study had limitations. A 72-h period might have led to misclassify the community- *vs.* hospital-acquisition of the viral infection since evidence suggests longer incubation periods [24]. Several factors contributing to disease severity and mortality including nursing home residency, frailty scores, bedridden status, immunization status, malnutrition, sarcopenia, presence of mixed viral and bacterial pneumonia, respiratory failure, occurrence of systemic complications and physicians' attitude towards more intensive care were not assessed. Moreover, our study lacks an assessment of post-discharge disability and follow-up.

In conclusion, this study provided one of the largest assessments available so far of clinical features and factors contributing to severity of illness in the oldest-old admitted with Influenza and/or RSV infections in Southern Europe. Chronic organ failure such as COPD or asthma and CKD predicted pneumonia and IHD, respectively, surpassing the importance of viral virulence. These findings could impact on public health policies such as fostering Influenza immunization campaigns, home-based care programmes [25] and end-of-life care. Filling knowledge gaps is crucial to set priorities and advise on transition model of care that best fits the oldest-old.

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Compliance with Ethical Standards

Funding: no funding was received for this study.

Conflict of Interest: the authors declare that they have no conflict of interest.

Ethical approval: This study was conducted in accordance with the Declaration of Helsinki. Formal ethical approval was obtained by the institutional review board of the coordinating centre (Central Lisbon Hospital Centre, no. 762_2019).

Informed consent: Informed consent was not deemed required for the purposes of this study.

References

1. Nielsen J, Vestergaard LS, Richter L, Schmid D, Bustos N, Asikainen T, et al. European all-cause excess and influenza-attributable mortality in the 2017/18 season: should the burden of influenza B be reconsidered? Clin Microbiol Infect 2019;25:1266-76. doi: 10.1016/j.cmi.2019.02.011.

2. Iuliano AD, Roguski KM, Chang HH, Muscatello DJ, Palekar R, Tempia S, et al. Estimates of global seasonal influenza-associated respiratory mortality: a modelling study. Lancet 2018;391:1285-300. doi: 10.1016/S0140-6736(17)33293-2.

3. Centers for Disease Control and Prevention. Disease Burden of Influenza. https://www.cdc.gov/flu/about/burden/index.html.

4. Nam HH, Ison MG. Respiratory syncytial virus infection in adults. BMJ 2019;366:l5021. doi: 10.1136/bmj.l5021.

5. Branche AR, Falsey AR. Respiratory syncytial virus infection in older adults: an under-recognized problem. Drugs Aging 2015;32:261-9. doi:10.1007/s40266-015-0258-9.

6. Haber N. Respiratory syncytial virus infection in elderly adults. Med Mal Infect 2018;48:377-82. doi: 10.1016/j.medmal.2018.01.008.

7. Vargas N, Tibullo L, Landi E, Carifi G, Pirone A, Pippo A, et al. Caring for critically ill oldest old patients: a clinical review. Aging Clin Exp Res 2017;29:833-45. doi:10.1007/s40520-016-0638-y.

8. Lund BD, Wang T. A bibliometric study of research pertaining to the oldest-old (age eighty-five and older). J Med Libr Assoc 2020;108:59-66. doi:10.5195/jmla.2020.762.

9. Topoulos S, Giesa C, Gatermann S, Fussen R, Lemmen S, Ewig S. Analysis of acute respiratory infections due to influenza virus A, B and RSV during an influenza epidemic 2018. Infection 2019;47:425-33. doi: 10.1007/s15010-018-1262-x.

10. Papadimitriou-Olivgeris M, Gkikopoulos N, Wüst M, Ballif A, Simonin V, Maulini M, et al. Predictors of mortality of influenza virus infections in a Swiss Hospital during four influenza seasons: Role of quick sequential organ failure assessment. Eur J Intern Med 2019. pii: S0953-6205(19)30460-1. doi:10.1016/j.ejim.2019.12.022.

11. Minney-Smith CA, Selvey LA, Levy A, Smith DW. Post-pandemic influenza A/H1N1pdm09 is associated with more severe outcomes than A/H3N2 and other respiratory viruses in adult hospitalisations. Epidemiol Infect 2019;147:e310. doi: 10.1017/S095026881900195X.

12. Ishiguro T, Kagiyama N, Uozumi R, Odashima K, Takaku Y, Kurashima K, et al. Clinical Characteristics of Influenza-Associated Pneumonia of Adults: Clinical Features and Factors Contributing to Severity and Mortality. Yale J Biol Med 2017;90:165-81.

13. Ishiguro T, Takayanagi N, Kanauchi T, Uozumi R, Kawate E, Takaku Y, et al. Clinical and Radiographic Comparison of Influenza Virus-associated Pneumonia among Three Viral Subtypes. Intern Med 2016;55:731-7. doi: 10.2169/internalmedicine.55.5227.

14. Korem M, Orenbuch-Harroch E, Ben-Chetrit E, Israel S, Cohen MJ, Sviri S, et al. Intensive Care Admissions and Associated Severity of Influenza B Versus A During Influenza B Vaccine-mismatched Seasons. Clin Infect Dis 2019;69:1049-52. doi: 10.1093/cid/ciz053.

15. Wang Y, Fan G, Horby P, Hayden F, Li Q, Wu Q, et al. Comparative Outcomes of Adults Hospitalized With Seasonal Influenza A or B Virus Infection: Application of the 7-Category Ordinal Scale. Open Forum Infect Dis 2019;6:ofz053. doi: 10.1093/ofid/ofz053.

16. Maruyama T, Fujisawa T, Suga S, Nakamura H, Nagao M, Taniguchi K, et al. Outcomes and Prognostic Features of Patients With Influenza Requiring Hospitalization and Receiving Early Antiviral Therapy: A Prospective Multicenter Cohort Study. Chest 2016;149:526-34. doi:10.1378/chest.14-2768.

17. Lee N, Lui GC, Wong KT, Li TC, Tse EC, Chan JY, et al. High morbidity and mortality in adults hospitalized for respiratory syncytial virus infections. Clin Infect Dis 2013;57:1069-77. doi: 10.1093/cid/cit471.

18. Lowery EM, Brubaker AL, Kuhlmann E, Kovacs EJ. The aging lung. Clin Interv Aging 2013;8:1489-96. doi: 10.2147/CIA.S51152.

19. Arabi YM, Fowler R, Hayden FG. Critical care management of adults with community-acquired severe respiratory viral infection. Intensive Care Med 2020;46:315-28. doi: 10.1007/s00134-020-05943-5.

20. Widmer K, Zhu Y, Williams JV, Griffin MR, Edwards KM, Talbot HK. Rates of hospitalizations for respiratory syncytial virus, human metapneumovirus, and influenza virus in older adults. J Infect Dis 2012;206:56-62. doi: 10.1093/infdis/jis309.

21. Sakamoto H, Ishikane M, Ueda P. Seasonal Influenza Activity During the SARS-CoV-2 Outbreak in Japan. JAMA 2020. doi: 10.1001/jama.2020.6173.

22. Kwon YS, Park SH, Kim MA, Kim HJ, Park JS, Lee MY, et al. Risk of mortality associated with respiratory syncytial virus and influenza infection in adults. BMC Infect Dis 2017;17:785. doi: 10.1186/s12879-017-2897-4.

23. Rochwerg B, Brochard L, Elliott MW, Hess D, Hill NS, Nava S, et al. Official ERS/ATS clinical practice guidelines: noninvasive ventilation for acute respiratory failure. Eur Respir J 2017;50. pii: 1602426. doi: 10.1183/13993003.02426-2016.

24. Lessler J, Reich NG, Brookmeyer R, Perl TM, Nelson KE, Cummings DA. Incubation periods of acute respiratory viral infections: a systematic review. Lancet Infect Dis 2009;9:291-300. doi: 10.1016/S1473-3099(09)70069-6.

25. Shepperd S, Doll H, Angus RM, Clarke MJ, Iliffe S, Kalra L, et al. Avoiding hospital admission through provision of hospital care at home: a systematic review and meta-analysis of individual patient data. CMAJ 2009;180:175-82. doi: 10.1503/cmaj.081491.

Table 1. Clinical features of oldest old population included in the study.

Oldest old patients (n)	251
Mean age ± SD (years)	89.4 ± 3.9
Male	31.5 (79)
Smoker	3.6 (9)
Diabetes	22.7 (57)
COPD or asthma	24.7 (62)
Obstructive Sleep Apnea or *Obesity hypoventilation syndrome*	4 (10)
CHF (class II NYHA or worse)	47 (118)
CKD (KDIGO 2012 stage 3A or worse)	19.5 (49)
Haematological neoplasm	3.2 (8)
Solid neoplasm	5.6 (14)
Type of virus infection	
Influenza-A	56.6 (142)
H1N1	12.7 (18)
H3N2	69 (98)
Unsubtyped	18.3 (26)
Influenza-B	15.9 (40)
RSV	25.9 (65)
Co-infection (Influenza-A+ Influenza-B)	1.2 (3)
Co-infection (Influenza-A+ RSV)	0.4 (1)
Pneumonia on presentation	32.3 (81)
Antiviral therapy with neuraminidase inhibitor	60.6 (152)
Non-invasively ventilated	8.8 (22)
Invasively mechanically ventilated	0.4 (1)
Hospital-acquired Influenza-A/B and/or RSV infection	12 (30)
Mean length of stay ± SD (days) of patients with community-acquired Influenza-A/B and/or RSV infection Median (IQR)	12 ± 11.1 9 (6-14)
Mean length of stay ± SD (days) of patients with hospital-acquired Influenza-A/B and/or RSV infection Median (IQR)	27.8 ± 28.7 20 (8-30)
In-hospital death	13.9 (35)
Patients with community-acquired Influenza-A/B and/or RSV infection	14 (31)
Patients with hospital-acquired Influenza-A/B and/or RSV infection	13.3 (4)

All data are shown as relative, %, and absolute (n) frequencies if not otherwise stated.

Abbreviations

COPD: chronic obstructive pulmonary disease; CHF: chronic heart failure; NYHA: New York Heart Association; CKD: chronic kidney disease; KDIGO: Kidney Disease: Improving Global Outcomes (2012); RSV: respiratory syncytial virus.

Table 2. Uni- and multivariable analyses for factors associated with pneumonia, non-invasive ventilation (NIV) and intra-hospital death in oldest old adults admitted with Influenza-A/B and/or RSV infection.

Characteristics	Outcome											
	Univariate analysis						Multivariable analysis					
	Pneumonia		NIV		Death		Pneumonia		NIV		Death	
	OR (95% CI)	*p*-value	OR (95% CI)	*p*-value	OR (95% CI)	*p*-value	OR (95% CI)	*p*-value	OR (95% CI)	*p*-value	OR (95% CI)	*p*-value
Age	0.95 (0.88-1.02)	0.151	1.04 (0.93-1.15)	0.485	1.04 (0.96-1.14)	0.341	0.96 (0.89-1.03)	0.246	1.05 (0.93-1.18)	0.436	1.05 (0.95-1.15)	0.334
Male	1.45 (0.83-2.54)	0.191	0.62 (0.22-1.73)	0.359	1.00 (0.46-2.15)	0.995	1.27 (0.71-2.30)	0.423	0.52 (0.16-1.68)	0.277	1.06 (0.47-2.40)	0.886
Diabetes	1.44 (0.78-2.66)	0.247	1.31 (0.49-3.52)	0.594	1.44 (0.64-3.20)	0.374	-	-	-	-	-	-
CHF (class II NYHA or worse)	0.74 (0.43-1.26)	0.270	2.10 (0.85-5.21)	0.108	2.10 (0.85-5.21)	0.108	-	-	-	-	-	-
CKD (KDIGO 2012 stage 3A or worse)	0.91 (0.46-1.78)	0.782	1.23 (0.43-3.53)	0.692	**2.52 (1.15-5.52)**	**0.020**	-	-	-	-	**2.50 (1.14-5.51)**	**0.023**
COPD or asthma	**1.93 (1.06-3.49)**	**0.030**	**3.49 (1.43-8.51)**	**0.006**	0.89 (0.38-2.07)	0.785	**1.86 (1.02-3.43)**	**0.045**	**4.40 (1.67-11.6)**	**0.003**	-	-
Type of virus infection												
Influenza-A	1	-	1	-	1	-	1	-	1	-	1	-
Influenza-B	0.89 (0.42-1.92)	0.774	2.76 (0.82-9.21)	0.100	1.72 (0.69-4.32)	0.246	0.90 (0.41-1.95)	0.782	**3.77 (1.06-13.5)**	**0.041**	1.77 (0.70-4.52)	0.231
RSV	1.14 (0.62-2.12)	0.672	**3.51 (1.27-9.68)**	**0.015**	1.11 (0.47-2.62)	0.817	1.16 (0.61-2.18)	0.654	**3.12 (1.09-8.92)**	**0.023**	1.11 (0.46-2.66)	0.813
Pneumonia on presentation	-	-	1.51 (0.62-3.69)	0.367	0.82 (0.37-1.79)	0.614	-	-	-	-	-	-
Hospital-acquired Influenza-A/B and/or RSV infection	0.60 (0.25-1.47)	0.264	0.33 (0.04-2.53)	0.286	0.94 0.31-2.89)	0.918	-	-	-	-	-	-

Abbreviations

NIV: non-invasive ventilation; CHF: chronic heart failure; NYHA: New York Heart Association; CKD: chronic kidney disease; KDIGO: Kidney Disease: Improving Global Outcomes (2012); COPD: chronic obstructive pulmonary disease; RSV: respiratory syncytial virus.