Clinical risk scores as predictors of severe outcome in hospitalized influenza patients: an observational cohort study from Norway 2014-2018

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Abstract

Background Seasonal influenza causes substantial numbers of hospitalizations annually, and there is a need to identify prognostic markers of clinical outcomes in hospitalized influenza patients. Methods Patients hospitalized with influenza were included during four influenza seasons (2014-2018). On admission, patients were assessed by the CRB65, CRB, SIRS and qSOFA risk scores. "Severe outcome" was defined as treatment in intensive care unit and/or all of the following three clinical parameters: pneumonia, O2 supplementation and hospital stay [?] 5days. Regression analyses were used to study effects of scores, influenza (sub)types and age on outcomes and treatment. Results A total of 156 patients with median age of 70 years were included. Patients with influenza A(H3N2) were older than those with B and A(H1N1). Older age was associated with fewer symptoms. Severe outcome was observed in 22% of the cases. High CRB, CRB65, SIRS and qSOFA scores at admission was observed in 60%, 46%, 40% and 29% of patients with severe outcome, respectively. Influenza (sub)types were not associated with severe outcome. Antiviral treatment was given to 37% of the patients, while 78% received antibiotics. The use of antiviral treatment increased during the study period. Patients with influenza B received less antiviral treatment. Conclusion This is the first study describing adult patients hospitalized with seasonal influenza in Norway. Risk scores, and particularly CRB, may be useful to predict severe outcome in influenza disease. More patients might have profited from antiviral therapy; including patients with influenza B infection.

Full title: **Clinical risk scores as predictors of severe outcome in hospitalized influenza patients: an observational cohort study from Norway 2014-2018**

Short title: **Influenza hospitalizations in Norway 2014-2018**

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Abstract

Background

Seasonal influenza causes substantial numbers of hospitalizations annually, and there is a need to identify prognostic markers of clinical outcomes in hospitalized influenza patients.

Methods

Patients hospitalized with influenza were included during four influenza seasons (2014-2018). On admission, patients were assessed by the CRB65, CRB, SIRS and qSOFA risk scores. "Severe outcome" was defined as treatment in intensive care unit and/or all of the following three clinical parameters: pneumonia, O2 supplementation and hospital stay [?] 5days. Regression analyses were used to study effects of scores, influenza (sub)types and age on outcomes and treatment.

Results

A total of 156 patients with median age of 70 years were included. Patients with influenza A(H3N2) were older than those with B and A(H1N1). Older age was associated with fewer symptoms. *Severe outcome* was observed in 22% of the cases. High CRB, CRB65, SIRS and qSOFA scores at admission was observed in 60%, 46%, 40% and 29% of patients with *severe outcome*, respectively. Influenza (sub)types were not associated with *severe outcome*. Antiviral treatment was given to 37% of the patients, while 78% received antibiotics. The use of antiviral treatment increased during the study period. Patients with influenza B received less antiviral treatment.

Conclusion

This is the first study describing adult patients hospitalized with seasonal influenza in Norway. Risk scores, and particularly CRB, may be useful to predict *severe outcome* in influenza disease. More patients might have profited from antiviral therapy; including patients with influenza B infection.

Keywords: Influenza, influenza subtype, antiviral, antibiotic, severity, clinical score, hospitalization, pneumonia

Introduction

Seasonal influenza is responsible for a substantial number of hospitalizations worldwide with high morbidity and mortality, particularly among the elderly (1, 2). In Norway, approximately 2500 patients are hospitalized

with influenza each season, giving an average seasonal incidence rate of 48 hospitalizations per 100 000 inhabitants (3). The World Health Organization (WHO) has defined that persons above 65 years, pregnant women and persons with chronic medical or immunosuppressive conditions are at greater risk of severe influenza disease or complications (1).

Two subtypes of influenza A (H1N1 and H3N2) and two lineages of influenza B (Yamagata and Victoria) have caused seasonal influenza during the last decade (1). While still under debate, influenza B has been suggested to cause less severe disease than the A subtypes (4-6). Whether various influenza types and subtypes are responsible for different clinical features is not clear, but influenza A(H3N2) is possibly associated with severe disease in persons above 65 years, whereas influenza A(H1N1) and B may affect younger persons (7-9).

Pneumonia in the setting of influenza disease occurs frequently and can be caused by the influenza virus itself or by bacteria such as *Streptococcus pneumonia* and *Staphylococcus aureus* (10). The discrimination between solitary viral pneumonia and pneumonia with bacterial coinfections is difficult. Thus, hospitalized influenza patients often receive antibiotic treatment, even when there is no obvious evidence of bacterial coinfections, possibly leading to unnecessary use of antibiotics (10, 11). In contrast, while international guidelines recommend that antiviral treatment with neuraminidase inhibitors always should be considered in patients hospitalized with proven or suspected influenza, such therapy may be underused (12-14).

As far as we are aware, there are no previous studies characterizing adult patients hospitalized with seasonal influenza in Norway. In this study we included patients hospitalized with influenza at a large university hospital between 2014 and 2018.

Our primary aim was to investigate whether established clinical risk score systems could predict severe outcome. Moreover, we also studied whether age and influenza types/subtypes (from here called (sub)types)) was associated with symptoms, risk scores, clinical outcomes and antimicrobial treatment.

Methods

Study setting, patients and inclusion

The study was conducted at Oslo University Hospital, Norway, during the four consecutive influenza seasons 2014-15 (S1), 2015-16 (S2), 2016-17 (S3) and 2017-18 (S4).

Patients [?] 18 years, with community-acquired influenza confirmed by in house influenza virus A/B RNA Real Time-PCR, were included within the first 3 days of hospitalization. There were no exclusion criteria.

Clinical data and scoring of disease severity

Patient data was collected by their respective physicians through patient interviews and from medical records. Patient characteristics, predisposing conditions (Table 1) and self-reported influenza vaccination status from the current season were recorded.

Nine influenza-specific self-reported symptoms were recorded (Table 2). We documented C-reactive protein (CRP) levels, radiological infiltrates on chest x-rays suggestive of pneumonia on admission (here defined as pneumonia), microbial findings from airway samples (nasopharyngeal swabs, sputum) and blood cultures. Diagnostics of respiratory pathogens in addition to influenza virus included bacterial cultures and in-house PCR panels for other respiratory viruses. Samples with detected influenza virus A were further analyzed with subtype-specific PCR to determine subtype H1 or H3. Further, treatment in ICU, need of oxygen supplementation, duration of hospital stay and antiviral and antibiotic treatment during hospital stay were registered.

The following four clinical risk scores were recorded at admission;

1) C onfusion, r espiratory rate, b lood pressure and age [?]65 years (CRB65) score; rewarding one point to each of the following signs: c onfusion, r espiratory rate [?]30/ min, systolic b lood pressure <90 mmHg or

diastolic b lood pressure [?]60 mmHg, and age[?]65 years (15). CRB65 [?] 2 points were defined as severe disease (CRB65^{high}) (15, 16).

2) CRB; a modified CRB65 with no points for age. CRB [?]1 was defined as severe disease (CRB^{high}).

3) S ystemic I nflammatory R esponse S yndrome (SIRS) score, rewarding one point to each of the following signs: Temperature >38degC or < 36degC, heart rate > 90 beats/min, respiratory >20 /min, leucocytes > 12,000/μL or <4000/μL. SIRS [?] 3 points was defined as severe disease (SIRS^{high}) (17).

4) The q uick S equential O rgan F ailure *A* ssessment (qSOFA) score, with one point for the following clinical signs: altered mental status, respiratory rate [?]22/ min, systolic blood pressure [?]100 mmHg (18). qSOFA [?]2 points were defined as severe disease (qSOFA^{high}).

Severe outcome of influenza as a combined clinical endpoint was defined as receiving treatment in ICU and/ or having all of the following three factors: Pneumonia on admission and oxygen supplementation during the hospital stay and staying in hospital [?]5 days.

Statistics

Differences in symptoms, clinical findings, severity scores, clinical outcomes and microbial treatment according to age, sex and influenza (sub)types were analyzed using Mann-Whitney U and Wilcoxon rank-sum tests for continuous variables, and Chi square test for categorical variables. We also used logistic regression to estimate odds ratios (ORs) with corresponding 95% confidence intervals (CIs) to study relevant exposures in relation to the various binary clinical outcomes or microbial treatment. For continuous variables, such as CRP and age, we used linear regression. All regression analyses were adjusted for age (except CRB65 scores), sex and having [?]2 predisposing conditions. Statistical analyses were performed with Stata/SE 15.0.

Ethics

The study was approved by The Regional Committee for Medical and Health Research Ethics in South Eastern Norway (Case number 2013/2033). Written informed consent was obtained from all participants before inclusion.

Results

Study participants

Patient characteristics and the distribution of influenza (sub)types are shown in Table 1. Overall, 156 patients (52.6% women) were included during the four influenza seasons from 2014-2018 (Seasons 1-4, respectively). The patients' median age was 70 year, 59.6% were 65 years or above. Predisposing conditions were common, 78.2% of patients had at least one predisposing condition, and 43.6% had [?]2 predisposing conditions. In contrast, only 21 patients (13.5%) were younger than 65 years and without any known predisposing conditions.

51 (32.7%) of the patients self-reported having received an influenza vaccine during the season they were hospitalized. Patients above 65 years were more often vaccinated (39.8%) as compared to patients below 65 years (22.2%; p=0.02).

Overall, most of the included patients had influenza A(H3N2) (52.6%), followed by influenza B (32.6%) and influenza A(H1N1) (12.8%). Three patients had influenza A of unspecified subtype (Table 1). In season 1 and season 3, most patients had influenza A(H3N2), while influenza A(H1N1) dominated among the included patients in season 2, and influenza B in season 4.

Clinical presentation and scores

The occurrence of self-reported symptoms before to hospitalization, and clinical risk scores on admission, and differences between older patients ([?]65 years) and younger patients (<65 years) are shown in Table 2. Cough (93.0 %) and fever (76.9 %), were the most commonly reported symptoms. Older patients reported less fever, sore throat and headache than younger patients. The number of reported symptoms was lower and reporting [?]5 symptoms were less frequent in older than in younger patients. The median duration of self-reported symptoms before admission was 3 days. Women reported more symptoms (median 6, range 2-9), than men (median 5, range 1-9) (p=0.017), and headache was the only specific symptom reported more often in women (63.4%) than men (40.5%) (p=0.004).

About $1/3^{rd}$ (34.6%) of the patients had a high CRB score, while CRB65^{high}, SIRS^{high}, and qSOFA^{high} were less common (Table 2). No patients below 65 year of age had CRB65^{high}, otherwise, the scores were comparable between the two age groups.

Biochemistry and microbiology

CRP on admission ranged from 0.6 to 316.0 mg/L, with a median of 42.5 mg/L.

Possible airway pathogen bacteria suggesting co-infections were found in 55 of the 150 patients (36.7%) with airway samples. *Streptococcus pneumoniae* was the most frequent bacteria found in 19 of the 150 patients (12.7%), followed by *Moraxella catharralis* (12.0%), *Haemophilus influenzae* (8.0%), and *Staphylococcus aureus* (6.0%). Other respiratory viruses than the index influenza virus were detected in airway samples from nine of the patients (5.8%), most frequently, respiratory syncytial virus which was found in four patients. Blood cultures were sampled from 136 (87.2%) of the patients, none of these were positive.

Clinical outcomes

A total of 35 patients (22.4%) had the combined *severe outcome* according to our definition (Table 3). Of these, nine patients (5.8%) were treated in ICU, pneumonia was found in 46.8%, 43.0% received oxygen supplementation during their hospital stay and 47.4% stayed in hospital [?]5 days. In general, patients with *severe outcome* were older than the rest (median age 75 vs 69, respectively, p=0.006) and were more likely to have cardiovascular disease, immunosuppression and [?]2 predisposing conditions (data not shown). Also, patients with *severe outcome* were significantly more likely to report dyspnoea and less likely to report sore throat, muscle pain and [?]5 symptoms (data not shown).

In multivariate analyses, older age, bacterial findings in airway samples and high CRP levels on admission were all associated with *severe outcome* (Table 3).

For the individual outcome factors, bacterial findings and high CRP levels were associated with pneumonia (Table 3). Older age, high CRP levels and female sex were associated with receiving oxygen during the hospital stay, and older age was associated with staying [?]5 days in hospital.

For all the risk scores, a high score on admission was associated with *severe outcome* in these influenza patients (Table 3). Among the patients classified with *severe outcome* , 60.0% had CRB^{high}, 45.7% had CRB65^{high}, 40.0% had SIRS^{high}, and 28.6% had qSOFA^{high} on admission.

For the individual outcome factors, CRB^{high} and CRB65^{high} were associated with treatment in ICU, pneumonia and oxygen supplementation. SIRS^{high} was associated with pneumonia and oxygen supplementation, but not with ICU treatment. CRB65^{high} was the only score associated with hospital stay [?]5 days, possibly because all of these patients were [?]65 years old. qSOFA^{high} was only associated with *severe outcome* , and not with any of the single factors.

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Influenza (sub)types

Patients with influenza A(H3N2) were significantly older (median age 72 years) than those with influenza B (median 64 years, p=0.032) and influenza A(H1N1) (median age 55 years, p=0.025). The frequency of symptoms according to influenza (sub)types is shown in Fig. 1A. Cough was more common in patients with influenza B and A(H3N2) than in patients with influenza A(H1N1). Patients with influenza B were more likely to report a sore throat than patients with influenza A(H3N2) and more rhinorrhea than patients with A(H1N1). These differences in symptom presentation between influenza subtypes were preserved in multivariate regression analysis (Supplementary table 1). Patients with influenza B tended to be more likely to report [?]5 symptoms than patients with A(H3N2) or A(H1N1) (Fig 1A and Supplementary table 1).

We found no significant differences in the risk scores CRB, qSOFA and SIRS between influenza (sub)types (Fig. 1B). More patients with influenza A(H3N2) had CRB65^{high} compared to patients with influenza B (p=0.002) and influenza A(H1N1) (p=0.042). However, with multiple regression analyses the difference in CRB65 score between A(H1N1) and A(H3N2) no longer appeared (Supplementary table 2).

Notably, neither the proportion of patients with our definition of *severe outcome* nor with pneumonia, oxygen supplementation or hospital stay [?]5days differed between influenza (sub)types. Similar results were found in multivariate regression analysis (Supplementary table 3). Influenza A(H3N2) was the only (sub)type found in patients admitted to ICU (n=9) (Fig 1C).

Antimicrobial treatment

During their hospital stay, 37.2% patients received antiviral treatment, all with oseltamivir (Table 4). 77.6% received antibacterial therapy and 49 patients (31.4%) received both type of treatments. Among patients with *severe outcome* , 40.0% received antiviral therapy and 91.4% received antibiotics. Benzylpenicillin was the most common initial antibiotic, given to 57.7% patients, in 14 of these in combination with gentamicin. In contrast, only 8.3% patients received a second or third generation cephalosporin. In multivariate regression analysis, patients with higher CRP levels and bacterial findings in airway samples on admission received more antibiotics (Table 4).

Patients with SIRS^{high} were more likely to receive antivirals than patients with low SIRS scores. Patients with CRB65^{high}, qSOFA^{high} and SIRS^{high} at admission tended to receive more antibiotics than patients with corresponding low scores, but the differences were not significant.

Patients defined as having *severe outcome* , were more likely to receive antibiotics, but not antivirals (Table 4). There was a trend that ICU treatment was associated with receiving antiviral therapy, but not with antibiotic treatment. Patients with pneumonia, or who received oxygen supplementation, or who stayed [?]5 days in hospital, received significantly more antibiotics, while no such differences were found for antivirals.

The use of antiviral treatment was significantly higher in season 3 (51.4%) than in season 1 (22.0%) (Fig. 2A and Supplementary table 4). The use of antibiotics was constant during the four seasons. Patients with influenza A(H3N2) received more antivirals than patients with influenza B (46.3% vs 25.5%, respectively (Fig 2B), and such an association was also found with multivariate regression analysis (supplementary table 4), also after additional adjustment for season (p=0.009). However, we observed no differences in antibiotic prescription between the influenza (sub)types.

Discussion

Here, we present clinical and microbiological characteristics and prognostic risk scores for *severe outcome* in adult hospitalized influenza patients during four consecutive influenza seasons 2014 -2018. About 85% of the patients were in a high-risk group for complicated influenza disease because of age and/or predisposing medical conditions. About one in four patients had clinical risk scores on admission indicating severe disease, and 22% had *severe outcome* according to our definition. The clinical score CRB^{high} showed the best

prediction for severe clinical outcome in these influenza patients irrespective of age, and seemed preferable to SIRS and qSOFA commonly used in clinical practice.

To study outcomes of influenza disease in hospitalized patients, different parameters such as in-hospital mortality, treatment in ICU, superinfections with pneumonia or other complications, and length of hospital stay have been used (6-9, 19, 20). Our definition of "severe outcome" may be debatable. The aim was to correctly identify patients that from a clinical perspective truly suffered from severe disease, and it is our opinion that having pneumonia, requiring oxygen or needing ICU treatment are clinical markers of severity.

Clinical scorings systems are frequently used to evaluate severe infections like community acquired pneumoniae and suspected sepsis (15, 18). To our knowledge, there are no established clinical scores for assessing disease severity at admission in hospitalized influenza patients. Scoring systems validated for evaluation of community-acquired pneumonia such as the pneumonia severity index (PSI) and the CURB65 score (a variant of CRB65 where levels of P-urea is also included) seem to have shown variable utility in prediction of outcome in hospitalized influenza patients (11, 21, 22). In present study, we found that high scores of CRB, CRB65, SIRS and qSOFA on admission were associated with *severe outcome* . Moreover, for patients with *severe outcome* , a high CRB score was found more frequently than any of the other high scores. Thus, we suggest that clinical severity scores, especially age-independent CRB, might be useful for the initial assessment and prediction of risk for*severe outcome* in patients hospitalized with influenza.

In the present study, influenza A(H3N2) was diagnosed in approximately half of the patients for the whole period with a predominance in the season 2016-2017. The influenza (sub)type distribution coincided with the virus (sub)types circulating in Norway and in Europe in the same time periods (1, 7, 8, 23).

In our patient population, comorbid conditions, especially cardiovascular and pulmonary diseases, were frequent, and the patients were also older than the participants in other recent studies with hospitalized influenza patients (5, 8, 9, 11, 19). We found that patients infected with influenza A(H3N2) were significantly older than patients with influenza B, while the patients with A(H1N1) were the youngest. This age distribution pattern has also been reported by others (7, 8, 19). In studies comparing patients with influenza A with influenza B without discriminating between the A subtypes, no age differences were reported (5, 6). It is not known why the elderly population seems to be more at risk for infection with influenza A(H3N2). However, combined effects of aging of the immune system (immunosenescence), influenza A(H3N2) virus evolving more rapidly than the other (sub)types and immune imprinting with A(H1N1) in the youth of today's elderly patients, may contribute (24-27).

Possible differences in disease severity between influenza(sub)types have been addressed in several previous studies with conflicting results (28, 29). In our study, we found no differences in CRB, SIRS and qSOFA scores between the influenza (sub)types. Patients with influenza A(H3N2) tended to have higher CRB65 scores on admission than patients with influenza B and A(H1N1), possibly explained with more A(H3N2) patients being older than 65 years. When studying the various clinical outcomes no differences between influenza (sub)types were found. Contrary to this, Delgado-Sanz *et al* recently reported more severe outcome in patients hospitalized with A(H1N1) compared to A(H3N2) and B (7), while Wang *et al* found that hospitalized patients with influenza B had less severe disease than influenza A patients (5). Yet other studies could not confirm such differences in disease severity between influenza (sub)types (8, 19, 30). Contradictory findings may at least partly be explained by methodological differences both in terms of patient inclusion and criteria for assessment of disease severity.

Cough and fever were the most common self-reported symptoms in our patient population, as observed in other studies in hospitalized influenza patients (6, 11, 19, 31). Patients above 65 years reported fewer influenza-suggestive symptoms than the younger patients, supporting that elderly patients present with a less specific clinical picture of influenza disease (19, 31, 32). In agreement with a previous study, women reported more numerous symptoms than men (31). For symptom presentation we found small differences between the influenza (sub)types, with influenza B patients reporting more cough and rhinorrhea than A(H1N1), and more sore throat than A(H3N2) patients. Other authors have reported less fever and more rhinorrhea in

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patients with influenza B than influenza A (sub)types (6, 9, 33). These data could suggest that influenza B may cause more "common cold" symptoms than the A subtypes; however, the clinical implications of these possible differences are uncertain, and several other studies could not find such differences (28).

Antibiotic therapy was given to almost 80% of our patient population, which corresponds well with previous studies on hospitalized influenza patients (11, 31). Clinical assessments using scoring systems could possibly be useful to guide antibiotic treatment in influenza patients. In our study, patients with high scores of CRB65, qSOFA and SIRS on admission tended to have more antibiotic treatment. We found that antibiotic treatment was also more frequent in patients with *severe outcome*, pneumonia, receiving oxygen supplementation or having higher CRP levels, or bacterial findings in airway samples, all factors that are indicative of bacterial coinfections. While CRP is a widely used biomarker to possibly discriminate between bacterial and viral infection, in the setting of influenza disease CRP discriminates poorly between pure viral and bacterial coinfections (34, 35). In contrast to findings in other studies, a majority of our patients received the narrow-spectrum antibiotic benzylpenicillin, reflecting the relatively restrictive recommendations for antibiotic prescription in the national guidelines, and relatively low level of antibiotic resistance in Norway (36).

Based on evidence from randomized and observational studies, international guidelines recommend antiviral treatment for all hospitalized patients with suspected or proven influenza disease (13, 37). In our study, less than 40% of the patients received antiviral therapy. Other studies from the same time period have shown a great variation of antiviral prescription rates in hospitalized patients, ranging from 12 to 93% (6-8, 19, 30). We found a trend of increasing use of antivirals from the 2014/15 and 2015/16 seasons to the 2016/17 season, suggesting increasing awareness of the beneficial effect of this treatment during the study period. We did not find any associations between prescription of antivirals and *severe outcome*, nor with the diagnosis of pneumonia or need of oxygen supplementation, indicating too little use of antivirals in this time period. Interestingly, we found that patients with influenza B received less antiviral therapy than patients with the influenza A subtypes. Similar differences were also reported in other studies (7, 30). However, as oseltamivir is approved for treatment of both influenza A and B and antivirals were part of the recommended therapy for all hospitalized influenza patients at the time of the study start, the reason for this difference is unclear. However, the observation could possibly be explained by patients with influenza A(H3N2) being older and probably more fragile with lower threshold for an aggressive therapeutic approach.

A strength of this study is that all patients had PCR-confirmed influenza. We also present the results adjusted for age, sex and having [?]2 predisposing factors, as adjusted results are lacking in many studies on influenza (sub)types and severity (28). Moreover, to our knowledge, this is the first study from Norway describing the clinical picture in adults hospitalized with seasonal influenza. By including patients over several seasons, we could study possible differences between influenza caused by different (sub)types and potential changes in antimicrobial treatment with time.

Our study has several limitations. First, few patients with influenza A(H1N1) were included, reducing the statistical power to explore differences between this (sub)type and the others. Second, we did not discriminate between the influenza B lineages Victoria and Yamagata, which may differ in their clinical presentation and severity (28). Third, the study was not designed to evaluate outcomes such as in-hospital and 30 days mortality. Forth, we were not able to include all the patients that were admitted to the hospital over the four seasons.

In conclusion, the patients in our study were elderly and/or with conditions predisposing for severe influenza infection. Clinical scoring systems seem to be useful to predict severe outcome, with the age-independent score CRB showing the most potential in this type of patients. The different influenza (sub)types were not associated with differences in clinical outcomes but we observed more influenza A(H3N2) in older than in younger individuals. There may have been an underuse of antiviral treatment in our patient population.

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Table 1. Patient characteristics and distribution of influenza (sub)types in included patients over the 4 consecutive influenza seasons

	Total	Season 1 2014-15	Season 2 2015-16	Season 3 2016-17
Patients, n (%)	156 (100)	41 (26.3)	28 (17.9)	35 (22.4)
Females, n (%)	82 (52.6)	23 (56.1)	15 (53.6)	15 (42.9)
Age, median [range]	70 [18-102]	74 [32-95]	55 [25-95]	71 [26-102]
Age [?] 65 years, n (%)	93 (59.6)	30 (73.2)	11 (39.3)	25 (71.4)
Predisposing conditions, n (%)				
Cardiovascular disease	75 (48.1)	25 (61.0)	8 (28.6)	20 (57.1)
Pulmonary disease	54 (34.0)	16 (39.0)	6 (21.4)	12 (34.3)
Diabetes	26 (16.7)	6 (14.6)	4 (14.3)	7 (20.0)
Immunosuppression	21 (13.5)	8 (19.5)	4 (14.3)	3 (8.6)
Neurological disease	18 (11.5)	6 (14.6)	0	6 (17.1)
Malignancies	10 (6.4)	5 (12.2)	4 (14.3)	1 (2.9)
Renal disease (GFR< 59 ml/min/1.73 m^2)	12 (7.7)	2 (4.9)	2 (7.1)	4 (11.4)
Obesity (BMI[?]30 kg/m^2)	8 (5.1)	4 (9.8)	2 (7.1)	1 (2.9)
Liver disease	3 (1.9)	0	2 (7.1)	1 (2.9)
Pregnancy	4 (3.0)	0	2 (7.1)	2 (5.7)
1 predisposing condition	122 (78.2)	35 (85.4)	19 (67.9)	30 (85.7)
2 predisposing conditions	68 (43.6)	24 (58.5)	7 (25.0)	18 (51.4)
No predisposing condition and age <65 year, n (%)	21 (13.5)	3 (7.3)	7 (25.0)	2 (5.7)
Seasonal influenza vaccination[a], n (%)	51 (32.7)	16 (39.0)	9 (32.1)	10 (28.6)
Influenza strains and subtypes, n (%)				
Influenza A(H3N2)	82 (52.6)	26 (63.4)	4 (14.3)	33 (94.2)
Influenza A(H1N1)	20 (12.8)	0	18 (64.4)	0
Influenza A na[b]	3 (1.9)	1 (2.4)	1 (3.6)	0
Influenza B	51 (32.6)	14 (34.1)	5 (17.9)	2 (5.7)

[a]Received seasonal influenza vaccine in the season they were hospitalized

[b]Subtype not available

Table 2. Self-reported symptoms before hospitalization and clinical risk scores on admission in patients below and [?]65 years of age

	Total	<65 years of age	[?]65 years of age	P value (chi2)
Patients, n (%)	156 (100.0)	63 (40.4)	93 (59.6)	-
Self-reported symptoms				
Cough, n (%)	145 (93.0)	61 (96.8)	84 (90.3)	0.120
Fever[a], n (%)	120 (76.9)	57 (90.5)	63 (67.7)	0.001
Dyspnea, n (%)	111 (71.2)	45 (71.4)	66 (71.0)	0.950
Muscle pain, n (%)	97 (62.2)	45 (71.4)	52 (55.9)	0.050
Sore throat, n (%)	90 (57.7)	45 (71.4)	45 (48.4)	0.004
Headache, n (%)	82 (52.6)	46 (73.0)	36 (38.7)	<0.001
Rhinorrhea, n (%)	62 (39.7)	28 (44.4)	34 (36.6)	0.323
Chest pain, n (%)	55 (35.3)	25 (39.7)	30 (32.3)	0.341
Gastrointestinal, n (%)	37 (23.7)	15 (23.8)	22 (23.7)	0.982
Number of symptoms, median [range]	5 [1-9]	6 [2-9]	5 [1-9]	0.0001[b]?¿?
5 symptoms, n (%)	98 (62.8)	51 (81.0)	47 (50.5)	<0.001
Clinical risk score at admission				
CRB[high], n (%)	54 (34.6)	19 (30.2)	35 (37.6)	0.336
CRB65[high], n (%)	35 (22.4)	0	35 (37.6)	<0.001
SIRS[high], n (%)	39 (25.0)	15 (23.8)	24 (25.8)	0.777
qSOFA[high], n (%)	22 (14.1)	7 (11.1)	15 (16.1)	0.377

[a]Measured or subjective

[b]Wilcoxon rank-sum test

Table 3. Clinical outcomes and associations with patient characteristics, laboratory data and clinical risk scores

Clinical outcomes

	Severe outcome[a]	Severe outcome[a]	Intensive care treatment	Intensive care treatment	Pneumonia on admission	Pneumonia on admission	Oxygen supplementation at any time	Oxygen supplementation at any time	[?]5 days in hospital
Patients, n (%)	35 (22.4)	35 (22.4)	9 (5.8)	9 (5.8)	73 (46.8)	73 (46.8)	67 (43.0)	67 (43.0)	74 (47.4)
	adjOR[b] (95% CI)[c]	P value	adjOR (95% CI) [c]	P value	adjOR (95% CI) [c]	P value	adjOR (95% CI) [c]	P value	adjOR (95% CI) [c]
Patients characteristic	Patients characteristic	Patients characteristic							
Age [cont.][d]	1.03 (1.01, 1.06)	0.018	1.02 (0.97, 1.06)	0.437	1.01 (0.99, 1.03)	0.180	1.03 (1.01, 1.05)	0.004	1.04 (1.02, 1.06)
Females	1.23 (0.56, 2.70)	0.608	0.76 (0.19, 2.99)	0.695	0.83 (0.44, 1.57)	0.565	1.99 (1.00, 3.93)	0.049	0.85 (0.43, 1.68)
[?]2 predisposing conditions	2.12 (0.94, 4.76)	0.071	2.26 (0.52, 9.87)	0.272	1.33 (0.68, 2.60)	0.41	1.63 (0.81, 3.27)	0.17	1.71 (0.84, 3.44)

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Laboratory data	Laboratory data								
Pos. bacterial airway samples at admission[e]	2.36 (1.03, 5.41)	0.042	1.70 (0.99, 1.01)	0.462	2.91 (1.44, 5.89)	0.003	1.67 (0.82, 3.41)	0.16	1.91 (0.91, 3.99)
CRP (mg/L) on admission [cont.][d]	1.01 (1.00, 1.01)	0.022	1.00 (0.99, 1.01)	0.517	1.02 (1.01, 1.02)	0.001	1.01 (1.00, 1.01)	0.015	1.00 (1.00, 1.01)
Clinical risk scores	Clinical risk scores	Clinical risk scores							
CRB[high]	3.51 (1.54, 8.00)	0.003	15.38 (1.84, 128.96)	0.012	2.57 (1.28, 5.16)	0.008	4.08 (1.93, 8.63)	<0.001	1.79 (0.86, 3.73)
CRB65[high,f]	3.72 (1.53, 9.01)	0.004	3.91 (0.89, 17.08)	*0.07*	3.61 (1.52, 8.57)	0.004	4.70 (1.93, 11.42)	0.001	2.83 (1.20, 6.69)
SIRS [high]	2.72 (1.14, 6.47)	0.024	0.80 (0.15, 4.14)	0.788	2.78 (1.28, 6.06)	0.010	5.14 (2.18, 12.12)	<0.001	1.58 (0.70, 3.56)
qSOFA[high]	3.19 (1.17, 8.70)	0.023	2.99 (0.66, 13.51)	0.156	1.68 (0.66, 4.29)	0.275	2.37 (0.87, 6.40)	0.09	1.95 (0.70, 5.46)

[a]*Severe outcome* is defined as receiving intensive care treatment and/or having all of the following three factors: pneumonia on admission + receiving oxygen supplementation during the hospital stay + staying [?]5 days in hospital

[b]Adjusted odds ratio

[c]Logistic regression analyses. Adjusted for age, sex and having [?]2 predisposing conditions

[d]Linear regression analysis: results given as regression coeffiecient (95% CI for the regression coefficient)

[e]6 patients did not have an airway sample for bacterial culture

[f]Not adjusted for age, as age is part of the score

Table 4. Antiviral and antibiotic treatment and associations with patient characteristics, laboratory data, clinical risk scores and clinical outcomes

	Antimicrobial treatment	Antimicrobial treatment	Antimicrobial treatment	Antimicrobial treatment
	Antiviral treatment	Antiviral treatment	Antibiotic treatment	Antibiotic treatment
Patients, n (%)	58 (37.2)	58 (37.2)	121 (77.6)	121 (77.6)

	Antimicrobial treatment	Antimicrobial treatment	Antimicrobial treatment	Antimicrobial treatment
	adjOR[a] (95% CI)[b]	P value	adjOR (95% CI)[b]	P value
Patient characteristics				
Age [cont.][c]	0.99 (0.98, 1.01)	0.491	1.00 (0.98, 1.02)	0.965
Females	1.28 (0.66, 2.47)	0.467	1.45 (0.68, 3.10)	0.339
[?]2 predisposing conditions	0.85 (0.42, 1.71)	0.648	1.24 (0.55, 2.77)	0.607
Laboratory data				
CRP (mg/L) on admission [cont.] [c]	1.00 (0.99, 1.00)	0.367	1.04 (1.02, 1.06)	<0.001
Bacterial findings on admission[d]	0.69 (0.34, 1.41)	0.311	3.18 (1.22, 8.32)	0.018
Clinical risk scores				
CRB high	1.36 (0.68, 2.74)	0.382	2.07 (0.86, 5.03)	0.106
CRB65[e] high	0.96 (0.41, 2.23)	0.929	2.85 (0.89, 9.14)	0.078
SIRS high	2.19 (1.03, 4.66)	0.041	3.03 (0.99, 9.31)	0.053
qSOFA high	0.33 (0.11, 1.04)	0.059	6.87 (0.88, 53.30)	0.065
Clinical outcomes				
Severe outcome[f]	1.33 (0.59, 3.00)	0.488	3.77 (1.05, 13.48)	*0.041*
Intensive care treatment	4.23 (0.99, 18.09)	0.050	0.95 (0.18, 4.89)	0.992
Pneumonia	1.05 (0.54, 2.05)	0.877	5.06 (2.02, 12.68)	0.001
Oxygen supplementation	1.81 (0.89, 3.66)	0.100	4.12 (1.61, 10.58)	0.003
[?]5 days in hospital	0.85 (0.42, 1.74)	0.663	2.67 (1.13, 6.34)	0.025

[a]Adjusted odds ratio

[b]Logistic regression analyses. Adjusted for age, sex and having [?]2 predisposing conditions

[c]Linear regression analysis: results given as regression coefficient (95% CI for the regression coefficient)

[d]6 patients did not have an airway sample for bacterial culture

[e] Not adjusted for age, as age is part of the score

[f]*Severe outcome* is defined as receiving intensive care treatment and/or having all of the following three factors: pneumonia on admission + receiving oxygen supplementation during hospital stay + staying [?]5 days in hospital

Figure legends

Figure 1

Symptoms, clinical risk scores and outcomes of disease and according to influenza (sub)types

A) Percentage of patients self-reporting specific symptoms prior to admission B) Percentage of patients with high clinical risk scores at admission defined by CRB, CRB65, SIRS and qSOFA criteria. C) Percentage of patients with various clinical outcomes of disease. *Severe outcome* is defined as receiving intensive care

treatment and/or having all of the following three factors: pneumonia on admission + receiving oxygen supplementation during hospital stay + staying [?]5 days in hospital.

Oxygen=oxygen supplementation and ICU=Intensive care unit. *indicates $p < 0.05$ and ** indicates $p < 0.01$ (chi2 analyses).

Figure 2

Use of antimicrobial treatment according to influenza season and influenza (sub)types

A) Percentage of patients receiving antiviral and antibiotic treatment over the 4 consecutive influenza seasons. For each treatment type, season 1 is compared with the other seasons. B) Percentage of patients receiving antiviral and antibiotic treatment according to their influenza (sub)types. *indicates $p < 0.05$ and ** indicates $p < 0.01$ (chi2 analyses).
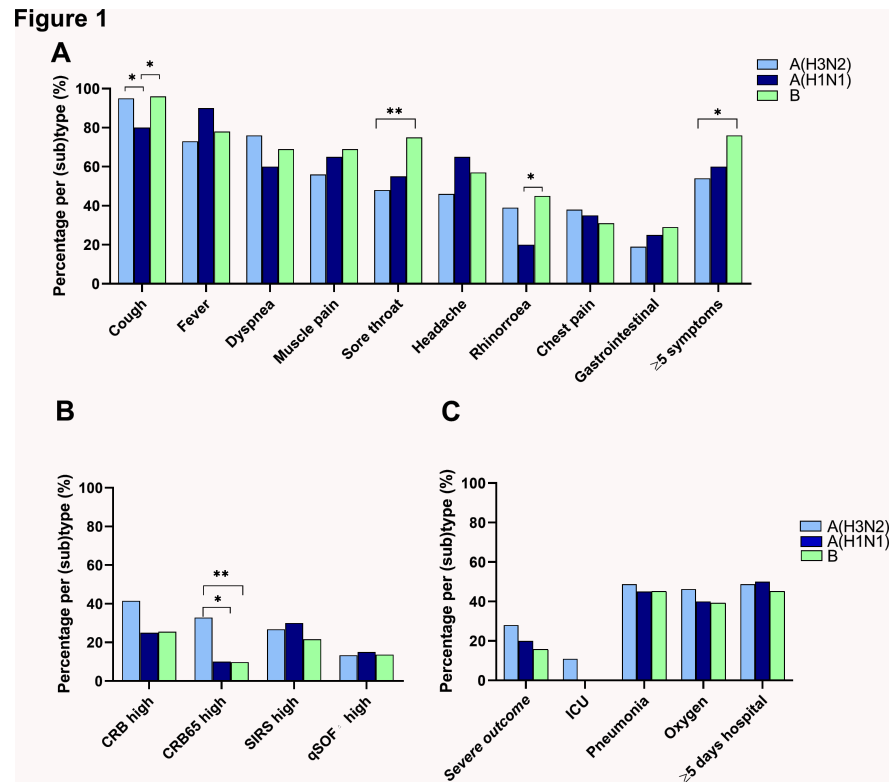
Figure 2

A

B