Diplomarbeit

Comparison of clinical presentation and laboratory values at admission between influenza-like disease (influenza PCR negative), PCR or NAAT confirmed influenza A and influenza B cases

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Graz, am 03.11.2021

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Glossar und Abkürzungen

ALT = Alanine aminotransferase

AST = Aspartate aminotransferase

BPM = Beats per minute

CK = Creatine Kinase

COPD = Chronic obstructive pulmonary disease

HA = Hemagglutinin

ICU = Intensive care unit

ILI = Influenza-like illness

INF A = Influenza A

INF B = Influenza B

LDH = Lactate dehydrogenase

NA = Neuraminidase

NAAT = Nucleic acid amplification test

PCR = Polymerase chain reaction

RIAT = Rapid influenza antigen test

RT-PCR = Reverse transcription polymerase chain reaction

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Abstract

Aim:

In our scientific thesis, data from patients infected with either influenza like illness, influenza A or influenza B were retrospectively analysed. The data were analysed for demographic data, hospitalization, outcome, medical imaging, clinical presentation, pre-existing medical conditions, physical examination, vital parameters and laboratory values. The aim was to evaluate differences or consistent patterns of the different diseases at first clinical presentation. A special focus was placed on influenza B.

Methods:

The study is a multicentre, non-randomised and retrospective data collection analysis. We included data from 2 case collectives, one from the winter season in 2009/2010 which included patients infected with influenza-like illness and influenza A. The other case collective was conducted in the winter season 2017/2018 and included patients infected with influenza A and influenza B. Our total patient population included 298 patients infected with influenza like illness, 246 patients with influenza A and 90 patients with influenza B. Due to the demographic distribution, some of the data were conducted with and some without patients under 18 years of age.

Results/Conclusion:

Firstly, in adults we observed a significant age difference between influenza like illness and the influenza-subtypes. The influenza B group was significantly older than the other groups. Secondly, our data showed that adult patients with influenza-like illness had a higher probability for hospitalization compared to patients infected with the influenza viruses. However, once hospitalised, patients suffering from influenza A we more likely to be transferred and cared for in the ICU than patients with influenza-like illness or influenza B. Adult influenza B patients were older and presumably more comorbid, nonetheless they had a lower hospitalisation rate, a lower intensive care unit admission rate and a lower in-hospital mortality than the younger influenza A patients.

Overall influenza B presented as a milder disease, however, annual vaccination with a quadruple vaccine is recommended for patients without contraindications. The influenza B virus should not be discounted, as serious courses may occur.

Zusammenfassung

Ziel:

In unserer wissenschaftlichen Arbeit wurden die Daten von Patient*innen, die entweder an einem grippalen Infekt, einer Influenza A oder Influenza B Infektion erkrankt waren, retrospektiv analysiert. Die Daten wurden im Hinblick auf demografische Daten, Krankenhausaufenthalt, Mortalität, medizinische Bildgebung, klinische Präsentation, Vorerkrankungen, körperliche Untersuchungen, Vitalparameter und Laborwerte analysiert. Ziel war es, Unterschiede oder einheitliche Muster der verschiedenen Krankheiten bei der ersten klinischen Vorstellung zu bewerten. Ein besonderer Schwerpunkt wurde hierbei auf die Influenza B gelegt.

Methoden:

Bei der Studie handelt es sich um eine multizentrische, nicht-randomisierte und retrospektive Datenerhebungsanalyse. Wir haben Daten aus zwei Fallkollektiven einbezogen, eines repräsentiert die Wintersaison 2009/2010 und umfasst Patient*innen mit grippalen Infekten und Influenza A. Das andere Fallkollektiv wurde in der Wintersaison 2017/2018 erfasst und beinhaltete Patient*innen mit Influenza A und Influenza B. Unsere gesamte Patientenpopulation umfasste 298 Patient*innen mit grippalem Infekt, 246 Patient*innen mit Influenza A und 90 Patient*innen mit Influenza B. Aufgrund der demografischen Verteilung wurden einige der Daten nur in Bezug auf erwachsene Patient*innen ausgewertet.

Ergebnisse/Schlussfolgerung:

Erstens wurde bei Erwachsenen ein signifikanter Altersunterschied zwischen grippalen Infekten und den Influenza-Subtypen festgestellt. Die Influenza-B-Gruppe war deutlich älter als die anderen Gruppen. Zweitens zeigten unsere Daten, dass erwachsene Patient*innen mit grippalen Infekten im Vergleich zu Patient*innen, die mit Influenzaviren infiziert waren, eine höhere Wahrscheinlichkeit für eine Krankenhauseinweisung hatten. Nach der Krankenhauseinweisung wurden Patient*innen mit Influenza A jedoch eher auf die Intensivstation verlegt und dort betreut als Patient*innen mit grippalen Infekten oder Influenza B. Erwachsene Influenza-B-Patient*innen waren älter und vermutlich stärker komorbid, dennoch hatten sie eine niedrigere Krankenhauseinweisungsrate, eine niedrigere Einweisungsrate auf die Intensivstation und eine niedrigere Sterblichkeit im Krankenhaus als die jüngeren Influenza-A-Patienten*innen.

Insgesamt stellte sich die Influenza B als eine mildere Erkrankung dar, dennoch wird eine jährliche Impfung mit einem Vierfachimpfstoff für Patient*innen ohne Kontraindikationen empfohlen. Das Influenza-B-Virus sollte nicht unterschätzt werden, da es ebenfalls zu schweren klinischen und tödlichen Verläufen kommen kann.

1 The Influenza Virus

Influenza is an acute respiratory illness mainly caused by influenza viruses A, B or rarely C occurring predominantly in the winter season (1). Typical symptoms are fever, headache, weakness, myalgia and cough. In healthy individuals influenza is usually self-limiting. In certain high-risk populations, however, influenza is associated with higher morbidity and mortality, (2) with secondary bacterial infections and nosocomial infections during hospitalization being a major risk factor for mortality. This thesis compares patients who were infected with either influenza-like illness (ILI), influenza A (INF A) or influenza B (INF B). The data was analysed for demographic data, laboratory values, clinical presentation, pre-existing medical conditions and outcome. Finally, the data was compared between ILI and the different influenza strains as well as between influenza A and B. The aim was to evaluate differences or consistent patterns of the different diseases. This diploma thesis puts a special focus on the influenza B virus.

1.1 About the Virus

The virus has been the subject to extensive research since it was first isolated from humans in 1933 (3). Vertebrates can be infected by various influenza viruses, however, in humans only influenza A, B and C cause infections (4). The genome of the virus consists of 8 individual RNA strands for influenza A and B; influenza C consists of 7 individual RNA strands (3). Furthermore, the surface glycoproteins hemagglutinin (HA) and neuraminidase (NA) are found in influenza A and B and play a crucial role in the transmission of the virus. For influenza A HA can be divided into 20 subtypes (H1-H20) and plays an important role in membrane fusion and receptor binding. The HA is largely responsible for virus entry into the host cell (5). In the past only H1-H3 strains were primarily responsible for infections in humans, recently however, new strains such as H5 and H7 have emerged.

Neuraminidase can be divided into 9 subtypes (N1-N9) it prevents viral aggregation and supports the movement through the mucus layer of the respiratory tract epithelium (6).

1.1.1.1 Transmission and characteristics of outbreaks

In infected individuals respiratory secretion is where most of the viral load is found. A high viral load can be detected especially at the onset of symptoms of the disease. The viruses can infect a new host via 2 routes. Firstly, transmission takes place through droplet infection. In this case, relatively large particles are distributed by infected persons

coughing or sneezing. Due to their size and weight these particles do not remain in the air for long, but sink to the ground, and can only be transmitted over short distances (7, 8). Secondly the virus can be transmitted via aerosols in the air. There is evidence for aerosol transmission or even transmission via the eye (7, 9). However, it is difficult to make precise statements about this route of infection for individual persons, as it depends on many factors such as the size of the room, breathing depth, duration of exposure, etc (7, 10-14).

1.2 Influenza B

Compared to influenza A, which infects a variety of different species with a wide range of subtypes, influenza B only has humans as a reservoir. However, influenza B viruses have been detected in Chincoteague Ponies and seals but without clinical relevance for humans (15, 16). Currently 2 circulating subtypes of influenza B exist, which are responsible for outbreaks at intervals of 2-4 years (17, 18). In contrast to influenza A, the influenza B virus has been relatively little investigated, which is partly due to its lack of pandemic potential. Nevertheless, the influenza B virus and its pathogenicity should not be underestimated (19). One paper place the mortality of influenza B infection between that of the H3N2 and H1N1 strains of influenza A, demonstrating that these can be serious infections (20). Overall, influenza B had a mortality rate of 29% of all influenza infections in the US from 1997 – 2009 (21).

Influenza B presents clinically in the same way as influenza A with symptoms such as cough, fever, and exhaustion. Thus, making it is impossible to determine a clinical difference between the two types of influenza (22). It should be added, however, that especially in children and young adults a more severe course of influenza B compared to influenza A is frequent (23, 24). Furthermore, septic shock is more common with influenza B. Mortality, 30-day mortality and mean length of hospital stay are relatively identical between the two groups (25).

1.3 Antigenic shift and antigenic drift

The influenza virus has a high mutation rate. Minor changes can be referred to as antigenic drift while major changes are called antigenic shift.

Antigen drift primarily arises from point mutations in the human genome, (26) mainly due to the RNA polymerase, which has no control mechanisms and therefore a high reproduction error rate (27). While many of these point mutations are insignificant and

cause only minute changes in proteins or the viral genome, it is still possible that the antigenic properties of the glycoproteins HA and NA are altered (28, 29). When mutations of the surface glycoproteins occur, they are immediately subject to selection pressure. Viruses with new antigenic properties evade pre-established immunity and thus gain a selection advantage (30, 31).
Antigenic shift results in complete HA or NA transmission, however, only happens in influenza A viruses, and is due to the large diversity of antigenic subtypes, which can be found in animal reservoirs (32). The result of antigen-shifting can be a high number of new infections because the human population has limited immunity to the new virus strain, holding the risk of a pandemic (33). Gradually, when partial immunity of the population is formed, the virus begins to return to its seasonal activity. Currently, almost all seasonal virus variants are descendants of former pandemic strains (34).

1.4 Diagnosis

In diagnostics we can differentiate between clinical and laboratory diagnosis. Both are important and support each other, as e.g., the pre-test probability can be increased. It is important to make the correct diagnosis early, as this will significantly improve the patients´ outcome, as it allows measures such as the correct use of antiviral drugs as well as infection control measures to be taken more effectively (35).

1.4.1 Clinical diagnosis

During seasonal outbreaks diagnosis can be made clinically based on typical clinical manifestations of the disease. In case of simultaneously occurrence of cough and fever, for example, the pre-test probability of influenza rises up to 79 % (36). One should not be influenced by an active vaccination status when deciding whether to use diagnostic tests. However, laboratory testing is only recommended when the result would change the measures (35). Since the emergence of SARS-CoV-2 disease, diagnosis of influenza based on signs and symptoms is no longer recommended because the symptoms of the diseases are too similar. Therefore, momentarily, laboratory-based diagnostics should be used to diagnose influenza.

1.4.2 Laboratory diagnosis

There are a variety of test procedures for laboratory diagnostics. They differ in the duration of evaluation, specificity, sensitivity, and availability of the tests. Some of the tests can be

used to detect subgroups of the various influenza viruses, such as H1N1. The choice of test depends largely on whether it has practical clinical relevance for treatment.

1.4.2.1 Molecular Assays

1.4.2.1.1 Reverse transcription- polymerase chain reaction (RT-PCR)

RT-PCR is still the gold standard for diagnosing influenza, as even the smallest amounts of virus can be determined, and a statement can be made about the infectiousness of the disease. Furthermore, it can be used for precise subtype identification. RT-PCR has the highest specificity and sensitivity of all test methods. One disadvantage, however, is that it can take up to 8 hours to perform the test, sometimes even longer, depending on availability and whether the sample must be analysed externally (35, 37, 38).

1.4.2.1.2 Rapid molecular assays

Due to the longer duration of PCR, faster molecular tests have been developed, which are also called rapid molecular assays. These tests can be performed directly in the outpatient clinic and the result is available within 30 minutes. They have a sensitivity of 92% but can only distinguish between influenza types A and B, and not between subtypes. The tests will continue to be referred to as nucleic acid amplification technology (NAAT) (39, 40).

1.4.2.2 Immunofluorescence

In immunofluorescence, the quality of the sample is crucial, but so are the skills of the laboratory staff. This why this method has been further developed over the past years, so that samples can now be analysed digitally. These digital immunoassays have a sensitivity of 80% for influenza A and 77% for influenza B. The results are available within 15 minutes, but again it is not possible to distinguish between individual subtypes of the influenza virus (39, 41).

1.4.2.3 Rapid antigen tests

Rapid antigen tests provide information on whether the patient is influenza positive or negative. It is not possible to differentiate individually at which stage of the disease a patient is in. The tests offer the advantage that the result is available after only 15 minutes and can be performed immediately in the outpatient clinic (42). The antigen tests have an average sensitivity of 62% and a specificity of 98% (43). They detect the virus best when a high viral load is present, which is especially the case in the early stages of the disease (44).

1.4.2.4 Viral culture

The viral culture takes 48-72 hours to achieve a result. This is too long a period in the clinical setting, as rapid diagnosis and treatment are critical for therapeutic success. For this reason, it is no longer used for clinical routine (45). However, the culture continues to be used in experimental laboratory testing as well as in non-clinical studies (35).

1.5 Prevention and Treatment

Treatment and prevention of the influenza virus infection can be divided into 3 main components, which are infection control, the use of antiviral medicines and vaccination. Each measure has a different treatment goal, be it to reduce symptoms or to prevent the spreading of the infection. In the following these different approaches as well as additional therapeutic concepts are discussed individually in detail.

1.5.1 Infection control:

Infection control measures include washing hands, wearing a mouth-nose mask, disinfecting surfaces, keeping hands away from mouth and nose as well as covering one´s cough (46). Hand hygiene and face masks could significantly reduce the transmission in household transmission, however the infection control measures had to be implemented within 36 hours of symptom onset (47). Correct and frequent hand washing led to a significant decrease in infections within 16 weeks in another study, (48) and staying at home for up to 24 hours after the fever subsides prevents the virus from spreading. An advantage of infection control in general is, that it can also protect against infection with other viruses such as the corona virus or rhinoviruses (46).

1.5.2 Antiviral medication

Patients who are ill with influenza do not always require antiviral therapy. One should always weigh the benefit and the risk well (49). Nevertheless, if therapy is started, it should be started as early as possible. The best effect is achieved if the therapy is administered within the first 48 hours after onset of the disease (35, 50). One study suggests, that in healthy individuals no benefit could be found when treatment was started after 48 hours (51). However, therapy can mitigate the individual course and prevent severe courses even if started after 48 hours. This is especially true for patients over 65 years of age and/or with multiple pre-existing illnesses (52). An indication for treatment and direct initiation of the therapy, regardless of illness duration, is given for patients hospitalized with influenza, for outpatients with a severe course as well as for patients belonging to an “at-risk” group (35). Patients in the at-risk group should be treated rather generously, (53-55) and includes

- Those ≥65 years of age
- Women who are pregnant or postpartum within two weeks after delivery
- Residents of long-term care facilities
- Those with extreme obesity (body mass index [BMI] ≥40)
- Individuals with certain chronic medical conditions (chronic lung disease, chronic heart disease, chronic kidney disease)
- Those receiving glucocorticoids or other immunosuppressive medications

Treatment with antiviral drugs should also be considered if the illness lasts less than 48 hours in the outpatient setting, as this may shorten the duration of illness. Furthermore, therapy should be considered in symptomatically ill patients, who have people in their environment who belong to the risk group. This is especially true for immunocompromised patients and health care workers (35).

1.5.2.1 Choice of antiviral therapy:

This is an overview of the treatment options with anti-viral drugs. Exact indications and individual therapies will not be deepened. Antiviral therapy can be divided into 3 different substance classes: adamantanes, Baloxavir and neuraminidase inhibitors. Since the use of adamantanes is discouraged by the Advisory Committee on Immunization Practices, it will not be covered further (49).

1.5.2.2 Neuraminidase inhibitors

For treatment with neuraminidase inhibitors 3 different drugs are currently available, these are Oseltamivir, Peramivir and Zanamivir. All 3 drugs reduce the duration and severity of the disease compared to placebo, (56) and the greatest benefit is achieved when therapy is started as early as possible.
Oseltamivir is the most prescribed drug for the treatment of influenza in Austria.
Oseltamivir can reduce the duration of illness by approximately one day if therapy is started early. Studies could show that mortality decreases with therapy (57-59). However, one study suggests that mortality reduction only applies to the H3N2 strain, but not to the H1N1 strain and influenza B (60).
Oseltamivir can also be given parenterally, but this approach is rather experimental and is not recommended for everyday clinical practice (61).

1.5.2.3 Bolaxavir:

Baloxavir is a new form of therapy that is currently only approved in Japan and the United States. It interferes with viral transcription by blocking the cap-dependent endonuclease (62, 63). Compared to the placebo group, the duration of the disease is effectively reduced by one day (64). At the moment, there are no studies comparing combination therapy with neuraminidase inhibitors in patients who belong to the risk group. Furthermore, it is not known whether Baloxavir is an alternative therapy for neuraminidase inhibitor-resistant influenza infections (65).

1.5.3 Vaccination

The vaccine acts by stimulating antibodies directed against the surface protein hemagglutinin (66). As explained in more detail above in the antigen shift and antigen drift section, the virus has constantly changing antigenic properties. For this reason, the vaccination must always be adapted to the new conditions every year. Since the process of vaccine production takes 6 months, a so-called mismatch may occur. An attempt is made to identify the future strains, but this is not always successful and the vaccination may thus be ineffective for the newly emerged strain (67). At present, there are triple and quadruple vaccines. The difference is that in the quadruple vaccine two strains of influenza group B are covered, and not only one. The quadruple vaccine is favorable, as in some cases high numbers of infections can occur due to seasonal influenza B infection (68). Due to the mismatches that occur, and which pose a risk of a pandemic, more universal vaccines are currently being developed to prevent this risk (69-71).

1.5.3.1 Indication and contraindication

Vaccination remains one of the best ways to protect against the disease and prevent its spread, which is why everyone should receive their annual dose of vaccine unless there are contraindications. Every person over 6 months of age should receive vaccination. Individuals at high risk (see list above) and medical personal should be given priority if there is a shortage of vaccine (67). It is only recommended to receive one dose of a vaccine per year (72). A contraindication is a severe allergic reaction to a previously received vaccination (67). Some adverse effects like a sore arm and bursitis of the deltoid muscle can occur, however do not account as contraindications (73, 74). A slightly increased number of Guillain-Barré Syndrome was observed after vaccination, but in total, this side effect is tolerable compared to the disease (75).

1.5.4 Additional therapy

There are some forms of therapy that can be given as additional treatment for influenza. However, there is insufficient data to suggest that these should be prescribed as standard and routine clinical practice.

1.5.4.1 Statins

Statins have an immunomodulating effect and have an anti-inflammatory effect. One study shows a correlation with lower mortality compared to not taking them. However, this was only done for seasonal influenza and only at one center, so more data are needed to support evidence (76).

1.5.4.2 Glucocorticoids

Glucocorticoids have an anti-inflammatory effect, which is why their use in influenza infections has been discussed for a long time. However, it has been shown that they may increase mortality, which is why their primary use is not recommended (77). However, they may have to be given for other indications (78).

1.5.4.3 Antibiotics

Antibiotics should be used if a secondary bacterial infection is suspected. This may be manifested by rapid deterioration of the patient, hypotension, or respiratory failure. The choice of antibiotic is best made depending on a sputum culture, but in severe courses direct empiric therapy should be started, which is effective against the most common pathogens. These are *Streptococcus pneumoniae*, *Streptococcus pyogenes* and *Staphylococcus aureus*. For empirical antibiotic therapy, a 3rd generation cephalosporin or fluoroquinolone is recommended. If an antibiotic-resistant germ is suspected, the therapy should be adjusted.

2 Material and methods

The study is a multicentre, non-randomised and retrospective data collection/analysis, which was conducted within the framework of a diploma thesis.

The Division of Pulmonology of the Department of Internal Medicine at the Medical University of Graz, Auenbruggerplatz 15, 8036 Graz, served as the study centre.

As the responsible ethics committee, reference should be made to the Ethics Committee of the Medical University of Graz, Auenbruggerplatz 2, 8036 Graz.

2.1 Literature research

In order to discuss the basic principles and the current state of science and research, reference was made not only to specialist books but also to national and international specialist studies, publications and articles from specialist journals. For literature research, mainly electronic databases such as PubMed, UpToDate and Google Scholar were used.

2.2 Data collection

Before data collection began, an ethics application was submitted to the Ethics Committee of the Medical University of Graz. It is expressly stated that the study is not connected with any commercial use and that there are neither financial nor academic conflicts of interest.
As part of a retrospective observational study, a query of the open MEDCOS system was conducted. Clinical parameters, laboratory chemistry parameters and imaging parameters were collected.

Clinical parameters included patient age, sex, clinical care, length of hospital stay, fever, cough, haemoptysis, dyspnoea, chest pain, myalgia/arthralgia, diarrhea, nausea/vomiting, rhinitis, headache, sore throat, fatigue, initial heart rate, systolic and diastolic blood pressure, wheezing/rales, height, weight, body mass index and outcome. Age at diagnosis was calculated from date of birth and date of testing. Furthermore, previous medical conditions such as bronchial asthma, chronic obstructive pulmonary disease, smoking history, coronary heart disease, heart failure, arterial hypertension, renal failure, diabetes, liver disease, malignant diseases, neurological diseases and pregnancy were screened. These parameters were obtained from the findings of the central emergency department.

Laboratory chemistry parameters collected include leukocytes (G/L), platelets (10^9/l), neutrocytes (%), eosinophils (%), monocytes (%), lymphocytes (%), CRP (mg/l), creatinine (mg/dl), gamma-glutamyltransferase (U/L), aspartate-aminotransferase (U/L), alanine-aminotransferase (U/L), creatine kinase (U/L), lactate dehydrogenase (U/L). The data were all collected on the day of admission and were taken and analysed as part of the routine laboratory.

For imaging procedures, it was determined whether a chest X-ray or computed tomography of the chest had been performed. Furthermore, new infiltrates were probed for. The data for this were obtained from the radiological reports.

2.3 Data analysis

Descriptive statistics as well as further analysis of the data took place using both Microsoft Office 365 Excel © and IBM SPSS Statistics © version 26. For all statistical procedures, the significance level α was set at 5% ($p < 0.05$). A test for normal distribution of the metrically scaled data was performed using the Kolmogorov-Smirnov test and the Shapiro-Wilk test. In each case, the differences between the cohorts were calculated using chi-square test, Kruskal-Wallis test or Analysis of variance according to Bonferroni.

2.4 Case collectives

2.4.1 Case collective 1

Inclusion Criteria:

- Patients with PCR positive/negative results who showed typical symptoms of an influenza infection
- All age groups

Exclusion Criteria

- Insufficient data material, missing information for statistical evaluation, insufficient/inaccurate documentation.
- Double entries

The patient data were collected from different hospitals in the Austrian province of Styria during the winter season in 2009/2010 and all refer to patients who presented first in

different emergency departments. The data includes patients of all ages, influenza A positive patients and patients with influenza-like-illness. No distinction is made between individual subtypes of influenza. The test results of this case collective were determined via polymerase chain reaction test. The data set consists of a total of 506 patients, of which 298 patients were assigned to the influenza-like-illness group and 208 patients to the influenza A positive group. Based on the epidemiological situation and retrospective analysis, we assume that these 208 patients were infected with the H1N1 subtype of influenza.

2.4.2 Case collective 2

Inclusion Criteria:

- Patients with nucleic acid amplification test (NAAT) positive results for Influenza A and Influenza B
- Patients ≥ 18 years

Exclusion Criteria:

- Insufficient data material, missing information for statistical evaluation, insufficient/inaccurate documentation.
- Double entries
- Patients < 18 years

The patient data were collected from the central emergency department at the Medical University of Graz in the winter season of 2017/2018 and all refer to patients who presented there first. The data includes only adult patients and only influenza positive patients. Here, only influenza A and B are distinguished, but not the different subgroups of these diseases. The test results of this case collective were determined via nucleic acid amplification test (NAAT). The data set consists of a total of 128 patients, of which 38 belong to the influenza A group and 90 to the influenza B group. Based on the epidemiological situation and retrospective analyses, we assume that these 38 patients of the influenza A group were infected with the H3N2 subtype of influenza.

3 Results

In the results section we analysed the combined data of the above case collectives. Our total patient population included 298 patients infected with ILI, 246 patients with influenza A and 90 patients with influenza B. Due to the demographic distribution, some of the data were conducted with and some without patients under 18 years of age. The patient population with patients ≥ 18 years of age consisted of 181 patients infected with ILI, 129 patients with influenza A and 90 patients with influenza B. Furthermore, for some analyses we performed a more specific analysis of the different influenza A subtypes. The subtype analysis refers to the H1N1 vs H3N2.

3.1 Gender distribution including all patients

Influenza-like illness showed a relatively even gender distribution with 154 male versus 144 female cases. Influenza A was diagnosed in more frequent in male patients (n=143) than in female patients (n=103). Influenza B showed an equal gender distribution with 45 cases, respectively. No statistically significant difference could be found. (p=0.346)

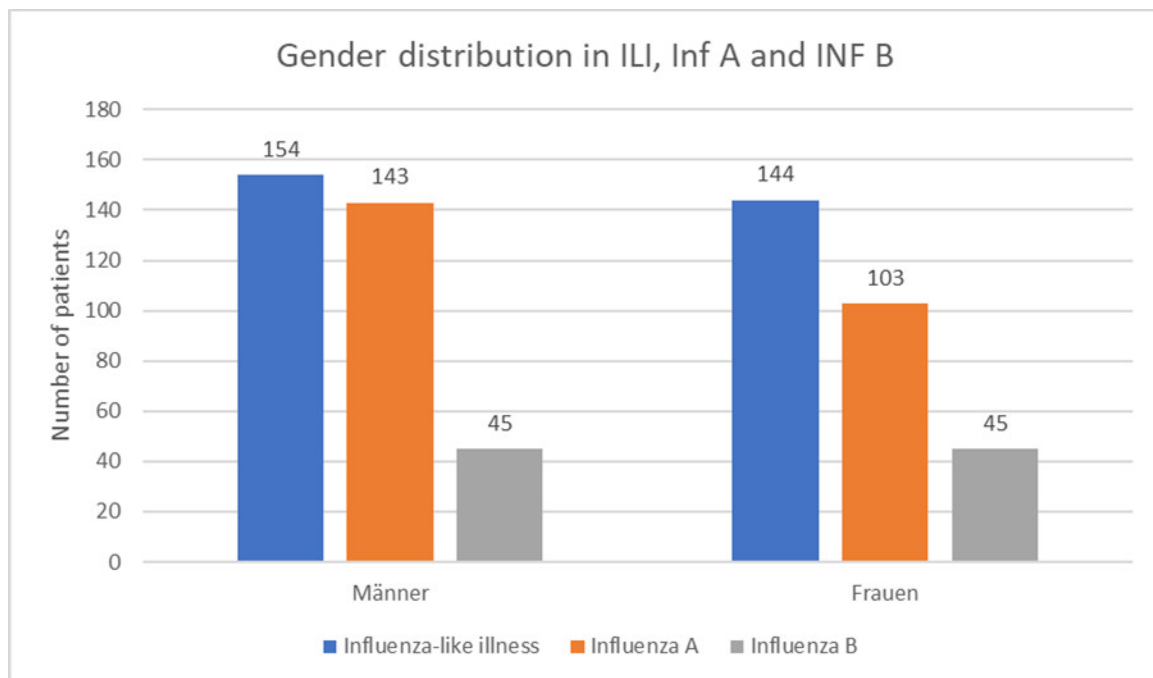


Figure 1 Gender distribution including all patients

3.1.1 Gender distribution of adult patients ≥ 18 years

Influenza-like illness showed a relatively even gender distribution with 93 male versus 88 female cases. Influenza A was diagnosed in more frequent in male patients (n=75, 58%) than in female patients (n=54, 42%). Influenza B showed an equal gender distribution with 45 cases, respectively. No statistically significant difference could be found. ($p=0.392$)

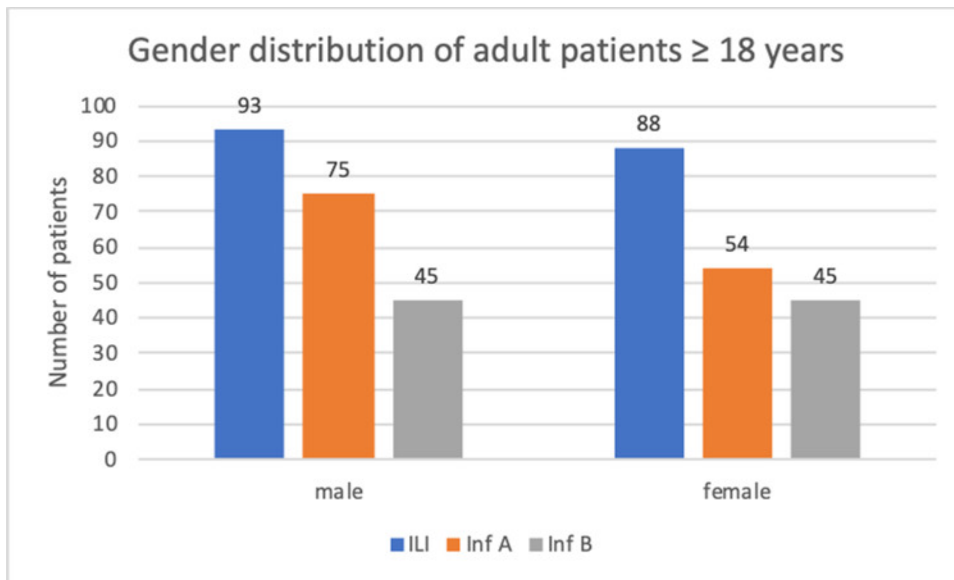


Figure 2 Gender distribution of adult patients ≥ 18 years

3.2 Age Distribution and mean age including all patients

Our study included patients from age 0 to age 92 for the ILI group, from age 0 to 87 for the influenza A group, and from age 18 to 95 for the Influenza B group. A statistically significant difference could be found ($p \leq 0.001$).

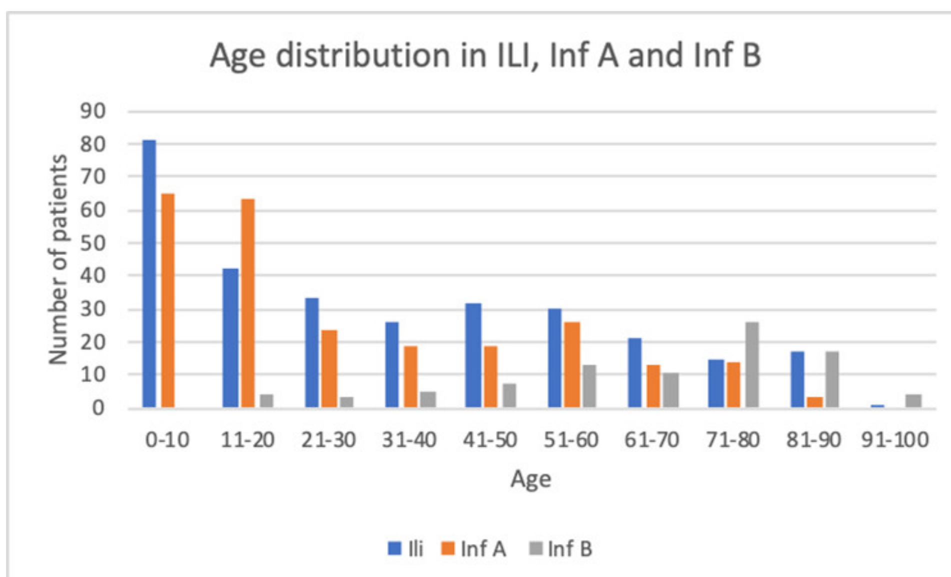


Figure 3 Age distribution including all patients

The mean age of the ILI group was 32.9 years compared to the mean age of 28.6 years for the influenza A group. The influenza B group showed the highest mean age with 65.3 years. A statistically significant difference between all groups ($p \leq 0.001$) was seen.

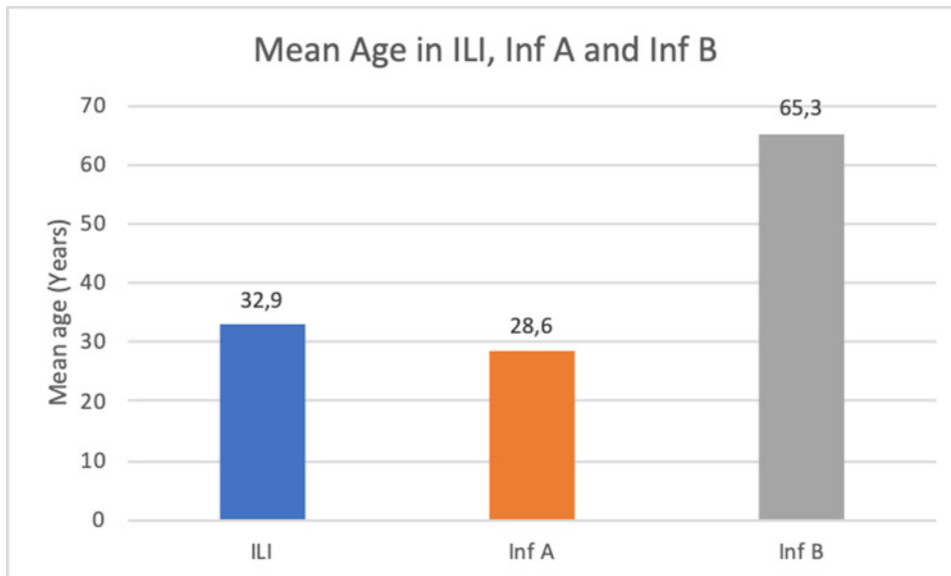


Figure 4 Mean age including all patients

3.2.1 Age distribution and mean age including only adult patients ≥ 18 years

Our study included patients from age 18 to 92 for the ILI group, from age 18 to 87 for the influenza A group, and patients from age 18 to 95 for the influenza B group. A statistically significant difference could be found comparing only adult patients. ($p \leq 0.001$).

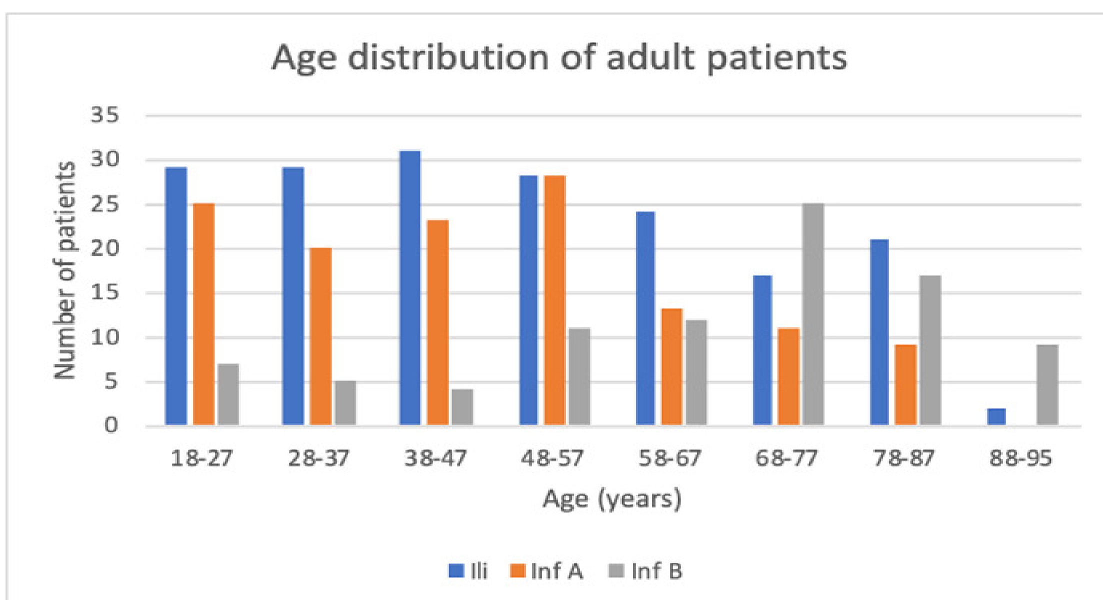


Figure 5 Age distribution of adult patients ≥ 18 years

The mean age of the ILI group was 49.9 years compared to a mean age of 43.5 years for the H1N1 group, and 53.8 years for the H3N2 group. The influenza B group showed the highest mean age with 65.3 years. A statistically significant difference was seen between all groups ($p = 0.04$).

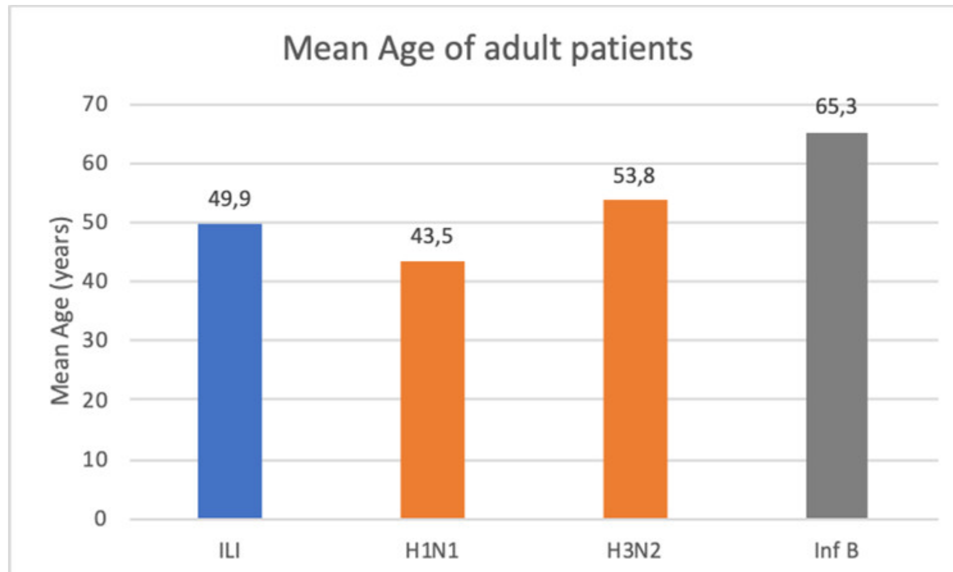


Figure 6 Mean age of adult patients ≥ 18 years

3.3 Hospitalization including all patients

The different groups showed a statistically significant difference in hospital admissions ($p \leq 0.001$). The hospital admissions were sub-classified into outpatients, inpatients and patients admitted to the intensive care unit. Regarding the intensive care unit, we included all patients regardless of when they were transferred to the intensive care unit.

Outpatients:

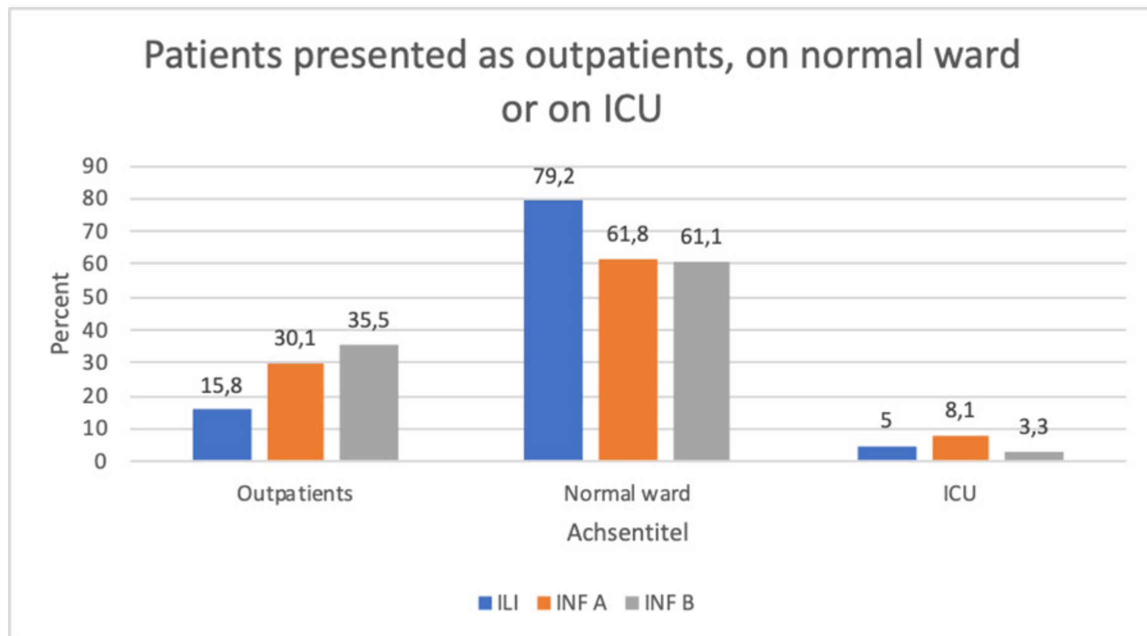
Patients of the ILI group were cared for as outpatients in 47/298 (15.8%) cases, representing the smallest group compared to 74/246 (30.1%) cases of the influenza A group and 32/90 (35.5%) cases of the influenza B group. Overall a significant statistical difference could be found between the groups ($p \leq 0.001$).

Normal ward patients:

Patients of the ILI group were cared for in normal ward in 236/298 (79.2%) cases, representing the largest group compared to 152/246 (61.8%) cases of the influenza A group and 55/90 (61.1%) cases of the influenza B group. Overall a significant statistical difference could be found ($p < 0.001$).

ICU patients

A statistically significant difference could be observed regarding admission to the intensive care unit (ICU) ($p<0.001$). 15/298 (5.0 %) patients from the ILI group were assigned to the ICU. The influenza A group showed the highest rate of all groups with 20/246 (8.1%) patients requiring intensive care. With 3/90 (3.3%) patients the group of influenza B infected patients had the lowest rate of patients requiring intensive medical care.



3.3.1 Hospitalization of adult patients ≥ 18 years

The different groups showed a statistically significant difference in hospital admissions ($p\leq0.001$). The hospital admissions sub-classified into outpatients, inpatients and patients admitted for the intensive care unit. Regarding the intensive care unit, we included all patients regardless of when they were transferred to the intensive care unit.

Outpatients:

Patients of the ILI group were cared for as outpatients in 26/181 (14.4%) cases, representing the smallest group compared to 35/129 (27.1%) cases of the influenza A group and 32/90 (35.6%) cases of the influenza B group. Overall a significant statistical difference could be found between the groups ($p\leq0.001$).

Hospitalization:

Patients of the ILI group were cared for as inpatients in 155/181 (85.6%) cases, representing the largest group compared to 94/129 (72.9%) cases of the influenza A group and 58/90 (64.4%) cases of the influenza B group. Overall a significant statistical difference could be found between the groups regarding overall hospitalization (p≤0.001).

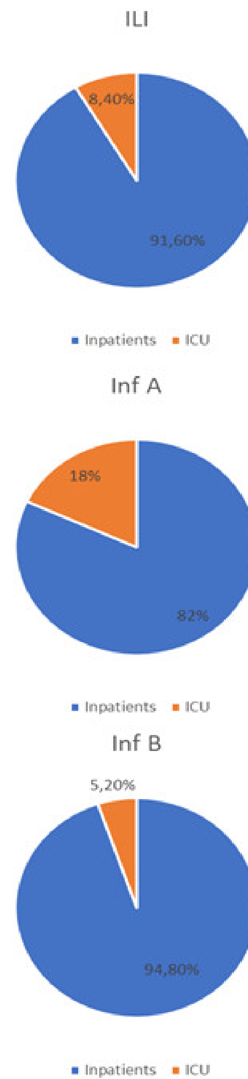


Figure 7 Hospitalisation of patients ≥ 18 years

Normal Ward

Patients of the ILI group were cared for in normal ward in 142/181 (78.5%) cases, representing the largest group compared to 77/129 (59.7%) cases of the influenza A group and 55/90 (61.1%) cases of the influenza B group. Overall a significant statistical difference could be found (p<0.001).

Intensive care unit

A statistically significant difference could be observed regarding admission to the intensive care unit (ICU) (p<0.001). 13/181 (7.2 %) patients from the ILI group were assigned to the ICU. The Influenza A group showed the highest rate of all groups with 17/129 (13.2%) patients requiring intensive care. With 3/90 (3.3%) patients the group of influenza B infected patients had the lowest rate of patients requiring intensive medical care.

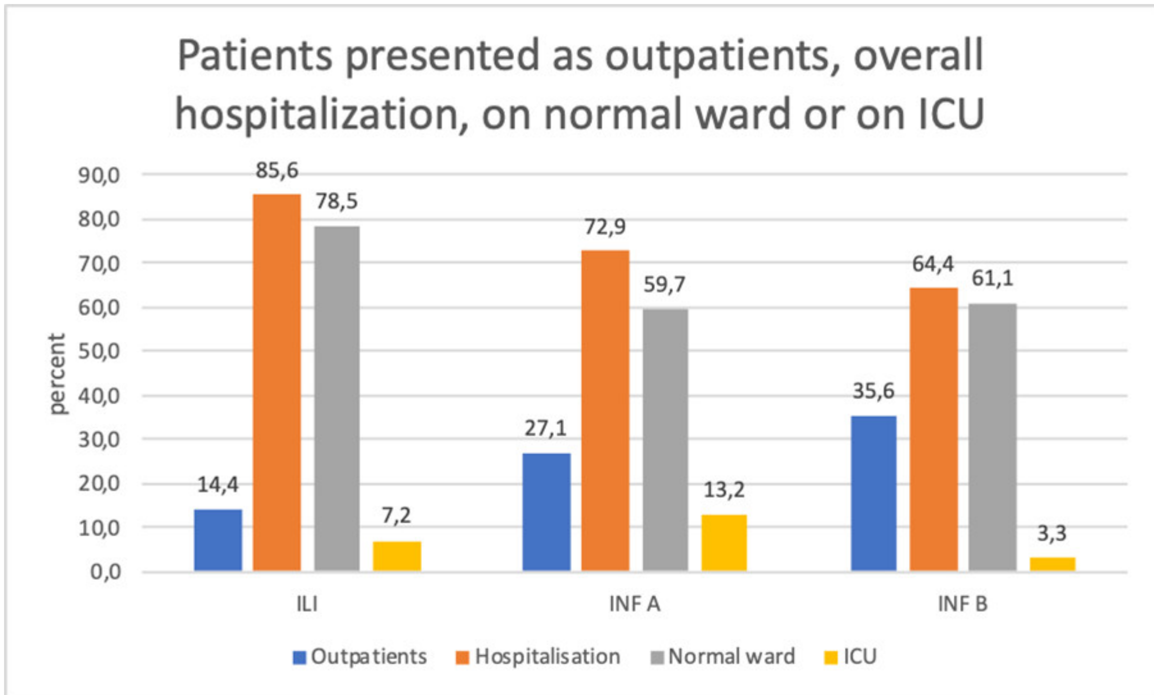


Figure 8 Hospitalization rate of adult patients ≥ 18 years

3.4 Outcome of adult inpatients ≥ 18 years

A difference could be found regarding the fatal outcome of adult inpatients. 8/155 (5.2%) ILI patients died during the course of their treatment, compared to 5/94 (5.3%) patients suffering from influenza A and 2/58 (3.4%) patients suffering from influenza B.

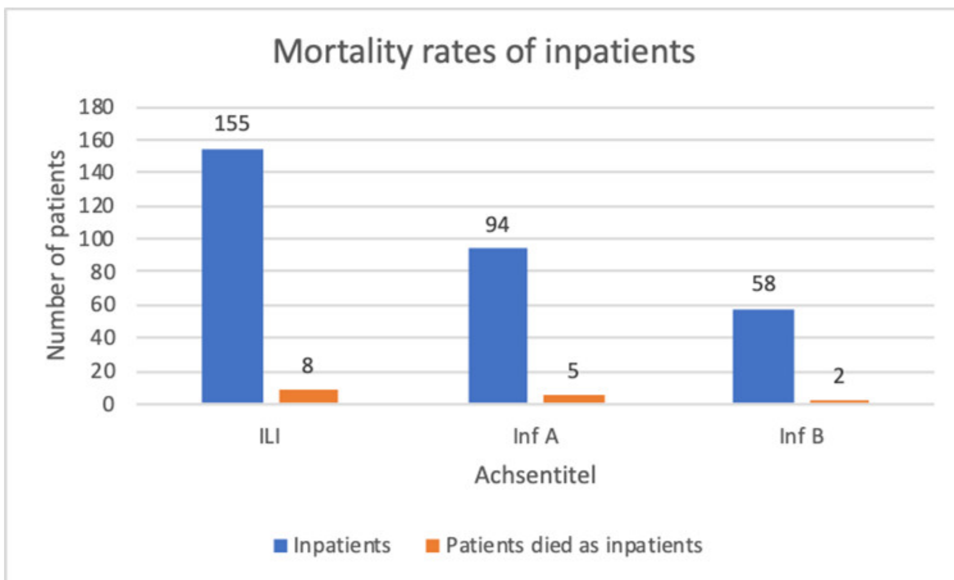


Figure 9 Mortality rates of inpatients ≥ 18 years

3.4.1 Outcome of adult patients in ICU ≥ 18 years

A difference could be found regarding the fatal outcome of adult patients admissioned to the ICU. 8/13 (61.5%) ILI patients died during the course of their treatment, compared to 5/17 (29.4%) patients suffering from influenza A. 2/3 (66.7%) patients suffering from influenza B died in the ICU which had the highest fatality rate in our groups.

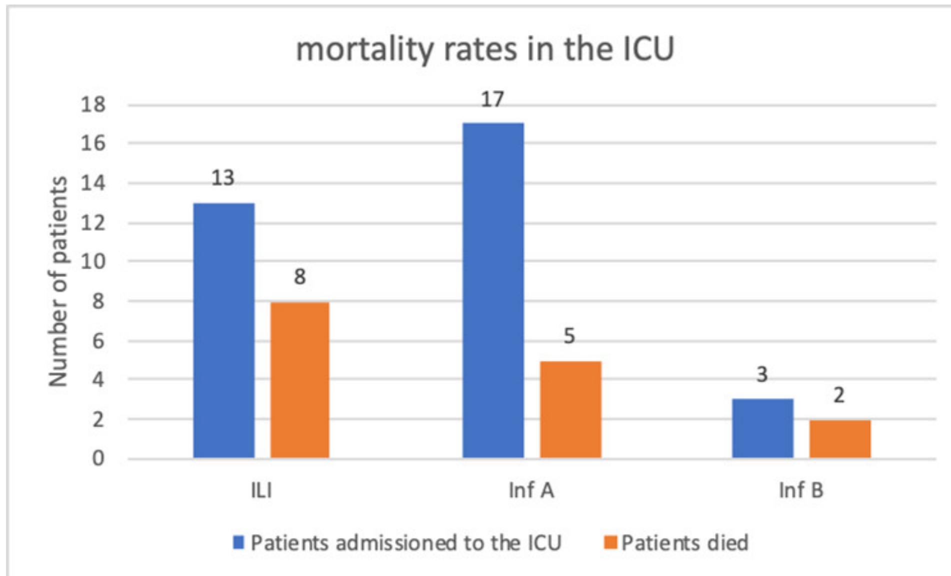


Figure 10 Mortality rates in the ICU for patients ≥ 18 years

	influenza-like illness	influenza A	influenza B	p-value
inpatients	155/181 (85.6%)	94/129 (72.9%)	58/90 (64.4%)	<0.001
patients died as inpatients	8/155(5.2%)	5/94 (5.3%)	2/58 (3.4%)	0.186
patients admissioned to the ICU	13/181 (7.2%)	17/129 (13.2%)	3/90 (3.3%)	<0.001
patients died in the ICU	8/13 (61.5%)	5/17 (29.4%)	2/3 (66.7%)	0.186

Table 1 Outcome of adult inpatients/ICU patients ≥ 18 years

3.5 Medical imaging including all patients

3.5.1.1 Chest X-ray

The amount of ordered chest X-rays showed a statistically significant difference between the three different groups ($p<0.001$). 218/298 (73.2%) of the ILI patients received medical imaging. Patients from the influenza A group were less likely to receive medical imaging with 151/246 (61.4%) ordered images, and patients from the influenza B group were most likely to receive medical images with 74/90 (82.2%).

Pulmonary infiltrates in the chest X-ray were described significantly more often in the ILI group (93/218, 42.7%) as compared to the influenza A group (47/151, 31.1 %), and patients of the influenza B group had the lowest probability (17/74, 23.0%) of demonstrating newly onset infiltrates.

Between the different influenza groups, a significant difference could be found for the ordered amount of chest X-rays ($p<0.001$).

3.5.1.2 Computed tomography of the thorax

For 39/298 ILI patients a computed tomography of the thorax was performed, showing newly onset pulmonary infiltrates in 21/39 (53.8%) cases. Of the 19/246 patients from the influenza A group who underwent computed tomography 15/19 (78.9%) showed newly onset infiltrates. In the influenza B group 8/90 (8.9%) patients received a computed tomography of the thorax. However, only in 2/8 (25.0%) patients newly onset infiltrates could be found. The three groups showed a statistically significant difference in the ordered amount of thorax-CT ($p=0.036$).

	influenza-like illness	influenza A	influenza B	p-value
ordered chest X-ray	218/298 (73.2%)	151/246 (61.4%)	74/90 (82.2%)	<0.001
chest X-ray with infiltrates	93/218 (42.7%)	47/151(31.1%)	17/74 (23.0%)	<0.001
ordered thorax-CT	39/298 (13.1%)	19/246 (7.7%)	8/90 (8.9%)	0.036
thorax CT with new infiltrates	21/39 (53.8%)	15/19 (78.9%)	2/8 (25.0%)	0.243

Table 2 Medical imaging including all patients

3.5.2 Medical imaging of adult patients ≥ 18 years

3.5.2.1 Chest X-ray of adult patients ≥ 18 years

The amount of ordered Chest x-rays showed no statistically significant difference between the three different groups (p=0.959). 149/181 (82.3%) of the ILI patients received medical imaging. Patients from the influenza A group received medical imaging in 107/129 (82.9%) cases, and in 74/90 (82.2%) cases patients from the influenza B group received medical imaging.

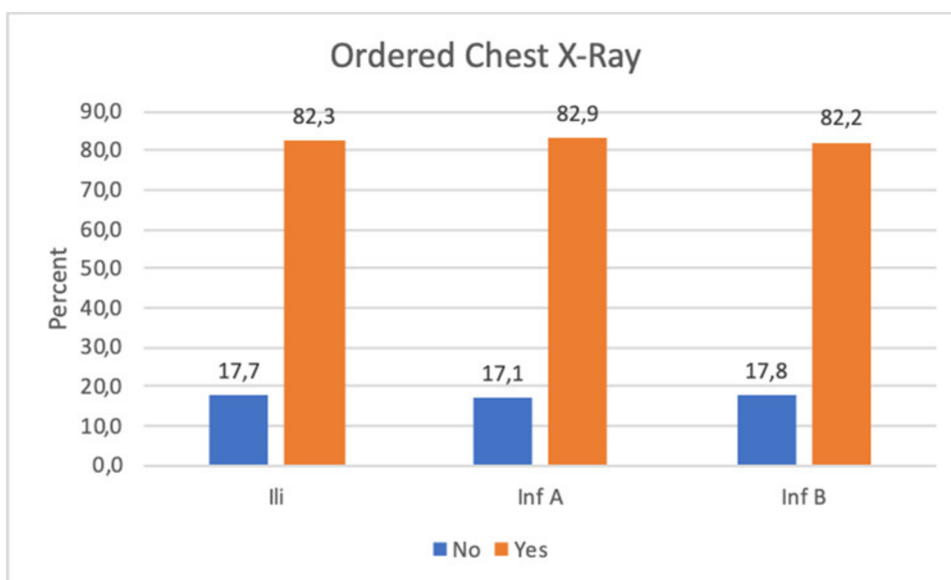


Figure 11 Ordered chest X-ray of adult patients ≥ 18 years

Newly onset pulmonary infiltrates found in the chest X-rays were described slightly more often for the ILI group with 56/149 (37.6%) cases, compared to 37/107 (34.6%) cases in the influenza A group. With 17/74 (23.0%) cases patients in the influenza B group had the lowest probability having newly onset infiltrates. Overall a significant difference could be found between the groups (p=0.048).

3.5.2.2 Computed tomography of the thorax of adult patients ≥ 18 years

In 39/181 (21.5%) ILI patients a computed tomography of the thorax was performed, demonstrating newly onset pulmonary infiltrates in 21/39 (53.8%) cases. 18/129 (14.0%) of the influenza A patients underwent computed tomography, of which 14/18 (77.8%) showed newly onset infiltrates. In the influenza B group 8/90 patients received a computed tomography of the thorax. However, in only 2/90 (25.0%) patients newly onset infiltrates could be found. The three groups showed a statistically significant difference in the ordered amount of thorax CT (p=0.019).

	influenza-like illness	influenza A	influenza B	p-value
ordered Chest x-ray	149/181 (82.3%)	107/129 (82.9%)	74/90 (82.2%)	0.959
chest X-ray with new infiltrates	56/149 (37.6%)	37/107 (34.6%)	17/74(23.0%)	0.048
ordered thorax CT	39/181 (21.5%)	18/129 (14.0%)	8/90(8.9%)	0.019
thorax CT with new infiltrates	21/39 (53.8%)	14/18 (77.8%)	2/8 (25.0%)	0.251

Table 3 Medical imaging of adult patients older than 17 years

3.6 Height, weight and Body Mass Index

The highly different age distribution in the three different groups prompted us to only compare patients at 18 years or older. The Ili group showed a mean height of 169.82cm which was the lowest compared to the influenza A group with 171.08 cm and 173.64 cm for the influenza B group, but without statistical significance (p = 0.111).

The mean body weight of the ILI group was 77.62 kg compared to the influenza A group with 79.32 kg, and therefore being the highest of all 3 groups, and 75.88 for the influenza B group with the mean lowest weight. No significant differences could be found (p = 0.879).

The ILI group showed a mean Body Mass Index of 26.79. The influenza A group showed the highest mean BMI of 27.11 and the influenza B group showed the lowest mean BMI with 25.57, but again without statistical significance (p = 0.529).

	influenza-like illness	influenza A	influenza B	p-value
height cm patients ≥ 18 years	169.82	171.08	173.64	0.111
Body Mass Index patients ≥ 18 years	26.79	27.11	25.57	0.529
weight kg patients ≥ 18 years	77.62	79.32	75.88	0.879

Table 4 Height, Weight and Body Mass Index

3.7 Signs and symptoms of first clinical presentation

The three groups showed a significant difference between the clinical sign fever as well as the clinical symptoms such as cough, nausea/vomiting, rhinitis, headache and fatigue. Details are listed in table 5 below. For some results a direct comparison between patients infected with H1N1 and those infected with H3N2 was made. A detailed overview can be found in table 5 below.

3.7.1 Fever

A Significant difference could be found regarding fever ($p<0.001$). Fever was defined as temperature over 38.0° Celsius axillary and/or intraauricular. 223/298 (74.8%) patients from the ILI group had fever during their admission in the hospital compared to 207/246 (84.1%) of the patients from the influenza A group, who were more likely to suffer from fever. Patients from the influenza B group suffered less fever with only 45/90 (50.0%) cases.

The direct comparison between the influenza A and influenza B group regarding fever showed a significant statistical difference ($p<0.001$).

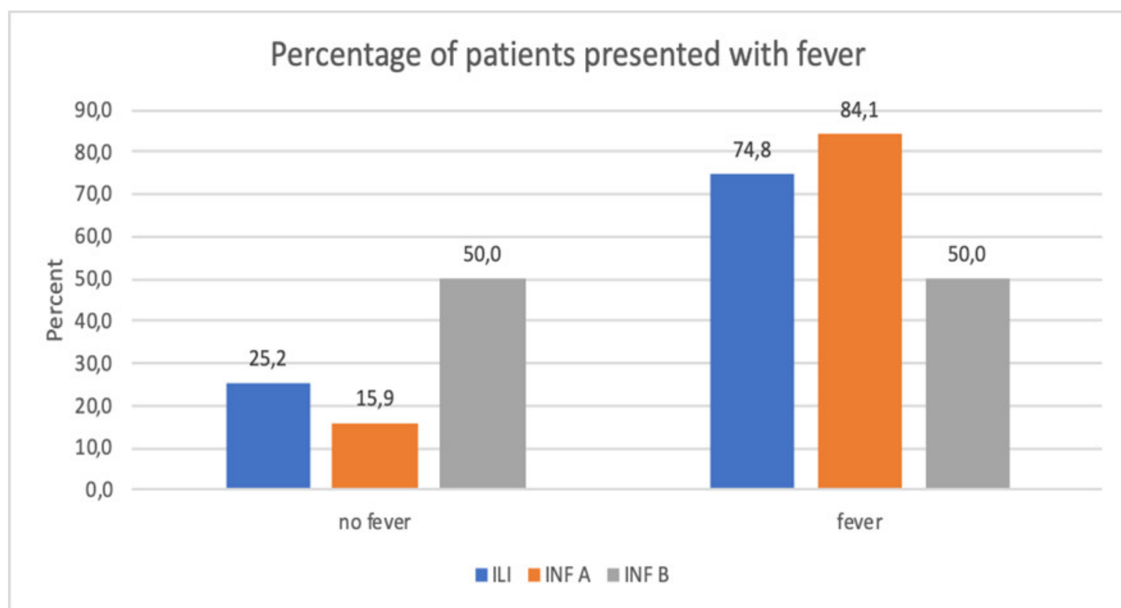


Figure 12 Percentage of patients presented with fever including all patients

3.7.2 Mean body temperature at hospital admission

For the mean body temperature, we have sub-divided the data of the influenza A group into a group of patients infected with H1N1, and into a group infected with H3N2. However, no significant difference could be found between all groups ($p=0.184$). The mean body temperature of the ILI group was 38.0° Celsius. The highest mean body temperature was seen for the H1N1 with 38.1° Celsius. Patients suffering from H3N2 had a mean body temperature of 37.7° Celsius. Influenza B patients showed a mean body temperature of 37.8° Celsius.

3.7.3 Headache

The ILI group showed 68/298 (22.8%) patients suffering from headache compared to 75/245 (30.6%) patients from the influenza A group. Patients from the influenza B group

were less likely to suffer from headache ($p \leq 0.001$), with only 8/90 (8.9%) patients stating the clinical symptom headache.

3.7.4 Fatigue

66/298 (22.1%) ILI patients presented with fatigue. 124/246 (50.8%) of the patients infected with influenza A were significantly more affected by fatigue, compared to the other groups ($p \leq 0.001$). In the influenza B group 15/90 (16.7%) patients suffered from fatigue.

3.7.5 Cough

All groups showed a significant difference in the clinical symptom of cough ($p < 0.001$). The ILI group presented with 152/298 (50.0%) cases and showed the lowest percentage of all groups. The influenza A group showed the highest number of cases with 182/246 (74.0%) presenting with cough, and the influenza B group presented with cough in 57/90 cases (63.3%). The direct comparison between the different influenza groups showed a significant difference ($p = 0.049$).

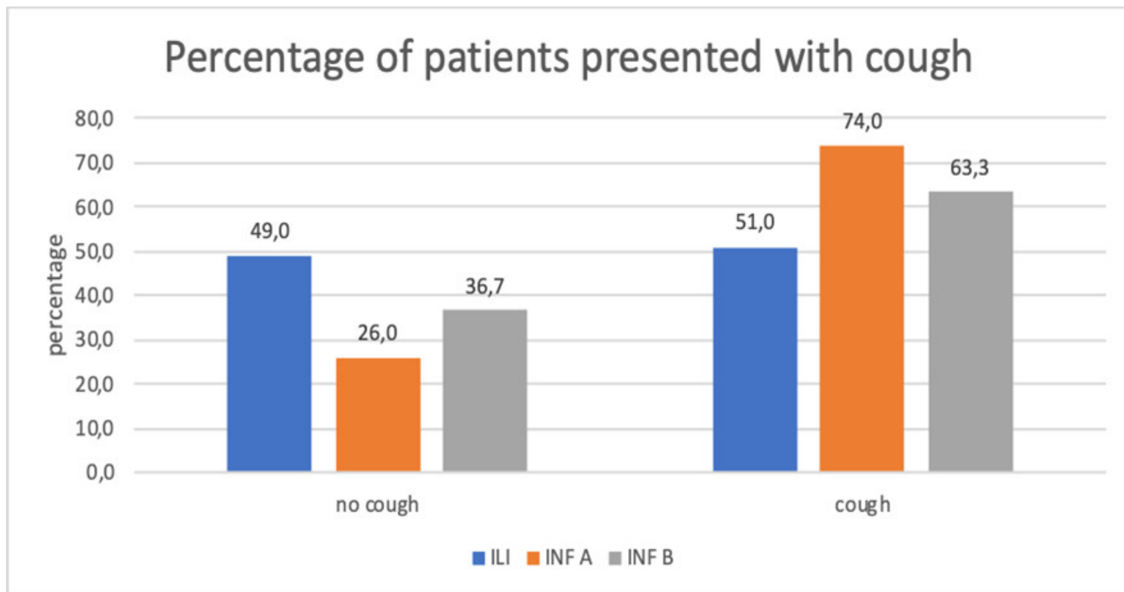


Figure 13 Percentage of patients presented with cough including all patients

3.7.6 Rhinitis

43/298 (14.4%) patients of the ILI group presented with rhinitis. With 52/245 (21.2%) patients from the influenza A group, patients infected with influenza A suffered significantly higher from rhinitis ($p = 0.002$). Only 5/90 (5.6%) of the patients from the influenza B group suffered from rhinitis.

3.7.7 Nausea/vomiting

In 84/298 (28.2%) cases patients of the ILI group presented significantly more frequent with nausea/vomiting compared to the other groups (p=0.032). 54/245 (22.0%) of the patients with influenza A patients suffered from nausea/vomiting, and only 14/90 (15.6%) of the patients infected with influenza B suffered from nausea/vomiting.

3.7.8 Other Symptoms

No significant differences could be found for dyspnea [57/298 (19.1%) ILI, 50/246 (20.4%) influenza A, and 16/89 (18.0%) influenza B (p=0.867)], diarrhea [37/298 (12.4%) ILI, 24/245 (9.8%) influenza A, and 10/90 (11.1%) influenza B (p=0.629), myalgia/arthralgia [63/298 (21.2%) ILI, 57/245 (23.3%) influenza A, and 17/90 (18.9%) influenza B (p=0.661).

	influenza-like Illness	influenza A	influenza B	p-value
fever	223/298 (74.8)	207/246 (84.1)	45/90 (50.0)	<0.001
headache	68/298 (22.8)	75/245 (30.6)	8/90 (8.9)	<0.001
fatigue	66/298 (22.1)	124/244 (50.8)	15/90 (16.7)	<0.001
cough	152/298 (50.0)	182/246 (73.98)	57/90 (63.3)	<0.001
rhinitis	43/298 (14.4)	52/245 (21.2)	5/90 (5.6)	0.002
nausea/vomiting	84/298 (28.2)	54/245 (22.0)	14/90 (15.6)	0.032
diarrhea	37/298 (12.4)	24/245 (9.8)	10/90 (11.1)	0.629

myalgia/arthralgia	63/298 (21.2)	57/245 (23.3)	17/90 (18.9)	0.661
dyspnoe	57/298 (19.1)	50/246 (20.4)	16/89 (18)	0.867

Table 5 Symptoms of first clinical presentation including all patients

3.8 Signs and symptoms of first clinical presentation for adult patients ≥ 18 years

We only analyzed results that were considered statistically relevant in the whole group and then performed a sub-analysis only of the adult patients. The three groups showed a significant difference between clinical sign fever as well as the clinical symptoms such as cough, headache and Fatigue. Comparing the whole group, the clinical symptoms rhinits and nausea/vomiting showed no significant difference. Details are listed in table 6 below.

3.8.1 Fever for adult patients ≥ 18 years

A Significant difference could be found regarding fever ($p<0.001$). Fever was defined as temperature over 38.0° Celsius axillary and/or intraauricular. 134/181 (74.0%) patients from the ILI group had fever during their admission in the hospital, compared to 97/129 (75.2%) of patients from the influenza A group, who were more likely to suffer from fever. Patients from the influenza B group suffered less fever with 45/90 (50.0%) cases.

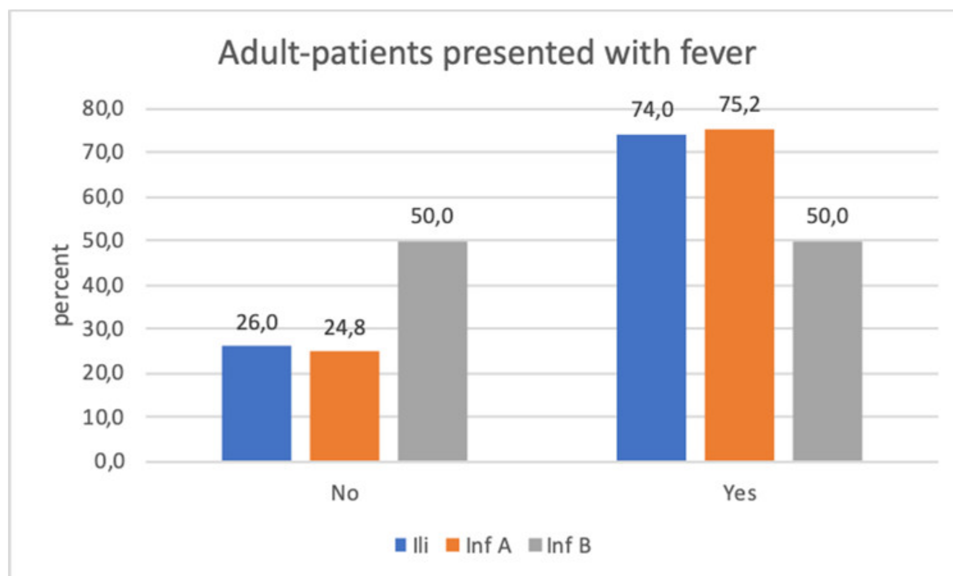


Figure 14 Fever for adult patients ≥ 18 years

3.8.2 Mean body temperature at hospital admission for adult patients ≥ 18 years

No significant difference could be found between all groups in regard to the mean body temperature at hospital admission for adult patients ($p=0.127$). The mean body temperature from the ILI group was 38.1° Celsius compared to a mean body temperature of 38.0° Celsius in the influenza A group. Patients suffering from influenza B had a mean body temperature of 37.8° Celsius.

3.8.3 Headache for adult patients ≥ 18 years

The ILI group showed 40/181 (22.1%) patients suffering from headache compared to 41/128 (32.0%) patients of the influenza A group. With only 8/90 (8.9%) patients stating the clinical symptom headache patients from the influenza B group were significantly less likely to suffer from headache ($p \leq 0.001$).

3.8.4 Fatigue for adult patients ≥ 18 years

45/181 (24.9%) ILI patients presented with fatigue. Patients infected with influenza were affected significantly more by the clinical symptom fatigue with 64/127 (50.4%) cases compared to the other groups ($p \leq 0.001$). In the influenza B group 15/90 (16.7%) patients suffered from fatigue.

3.8.5 Cough for adult patients ≥ 18 years

All groups showed a significant difference for adult patients in the clinical symptom of cough ($p<0.001$). The ILI group presented with 84/181 (46.4%) cases and showed the lowest percentage of all groups. The influenza A group showed the highest amount with 98/128 (76.6%) clinical cases with cough and the influenza B group presented with cough in 57/90 cases (63.3%).

3.8.6 Rhinitis for adult patients ≥ 18 years

6/181 (3.3%) patients of the ILI group presented with the clinical symptom of rhinitis. With 11/128 (8.6%) cases, patients from the influenza A group suffered more often from rhinitis, however without a statistical difference ($p=0.135$). Only 5/90 (5.6%) patients from the Influenza B group suffered from the clinical symptom rhinitis.

3.8.7 Nausea/Vomiting for adult patients ≥ 18 years

With 37/181 (20.4%) adult patients presenting with nausea/vomiting the ILI group was affected more frequent than the other groups, however without significant difference ($p=0.573$). 22/128 (17.2%) patients from the influenza A patients suffered from

nausea/vomiting. With 14/90 (15.6%) cases, patients infected with Influenza B where less likely to suffer from Nausea/Vomiting.

	influenza-like Illness	influenza A	influenza B	p-value
fever	134/181 (74.0%)	97/129 (75.2%)	45/90 (50.0%)	<0.001
headache	40/181 (22.1%)	41/128 (32.0%)	8/90 (8.9%)	<0.001
fatigue	45/181 (24.9%)	64/127 (50.4%)	15/90(16.7%)	<0.001
cough	84/181 (46.4%)	98/128 (76.6%)	57/90 (63.3%)	<0.001
rhinitis	6/181 (3.3%)	11/128 (8.6%)	5/90 (5.6%)	0.135
nausea/vomiting	37/181 (20.4%)	22/128 (17.2%)	14/90 (15.6%)	0.573

Table 6 Symptoms of first clinical presentation for adult patients ≥ 18 years

3.9 Past medical history

For the past medical history only patients at age of at least 18 were included in the results due to the demographic distribution. Details are listed in table 7 below.

3.9.1 Liver diseases

A history of liver disease could be found in 32/181 (17.7%) patients of the ILI group, being significantly more frequent than in the influenza A group with 7/127 (5.5%) cases, and in the influenza B group with 5/90 (5.6%) cases (p<0.001).

3.9.2 Cardiovascular diseases

In the ILI group 30/180 (16.7%) patients showed a history of coronary heart disease compared to 13/127 (10.2%) patients in the Influenza A group, and 8/90 (8.9%) patients in the influenza B group. No significant difference between the groups could be found regarding coronary heart disease (p=0.112).

Significant differences could be found for the history of cardiac insufficiency as well as for a history of arterial hypertension. 25/181 (13.8%) of the ILI patients, 7/127 (5.5%) patients of the influenza A group, and 3/90 (3.3%) patients of the influenza B group showed a history of cardiac insufficiency (p=0.005). The number of patients suffering from arterial hypertension was significantly higher in the Influenza B group 45/90 (50.0%), compared to 71/181 (39.2%) patients of the ILI group and 36/127 (28.3%) patients of the influenza A group (p=0.005).

3.9.3 Pregnancy

Within the ILI-group, 6/181 (3.3%) patients where pregnant compared to 12/127 (9.4%) patients in the Influenza A group and 1/90 (1.1%) patients for the influenza B group. Overall a statistically significant difference could be found between the 3 groups (p=0.008).

3.9.4 Chronic renal failure and Diabetes Mellitus

Between the groups no significant statistical difference could be found for the number of patients suffering from chronic renal failure (p=0.057). 35/181 (19.3%) patients of the ILI group suffered from chronic renal failure compared to 12/127 (9.4%) patients of the influenza A group, and 13/90 (15.1%) patients of the influenza B group. No significant difference could be found regarding the history of diabetes mellitus. 25/181 (13.8%) patients of the ILI group, 12/127 (9.4%) patients of the influenza A group, and 9/90 (10.0%) patients of the influenza B group suffered from diabetes mellitus (p=0.435).

3.9.5 Lung diseases

12/181 (6.6%) of the ILI patients, 11/127 (8.7%) of the influenza A patients, and 2/90 (2.2%) of the influenza B patients showed a history of asthma bronchiale (p=0.151). A history of chronic obstructive pulmonary disease (COPD) could be found in 19/181 (10.5%) patients of the ILI group, and in 17/127 (13.4%) patients of the influenza A group. With 14/90 (15.6%) patients having a history of COPD the influenza B group was most likely to have a history of COPD (p=0.469).

No significant difference could be found regarding for the history of smoking. 29/181 (16.0%) patients of the ILI group, 18/127 (14.2%) patients of the Influenza A group, and 9/90 (10.0%) patients of the influenza B group showed current nicotine consumption.

3.9.6 Other diseases

A history of liver disease could be found in 32/181 (17.7%) patients of the ILI group, being significantly more frequent than in the influenza A group with 7/127 (5.5%) cases, and in the influenza B group with 5/90 (5.6%) cases ($p<0.001$)
No significant differences could be found for malignancies and neurological diseases. Malignancies presented with 17/181 (9.4%) cases in the ILI group, 13/127 (10.2%) cases in the influenza A group, and 12/90 (13.3%) in the influenza B group ($p=0.604$). Neurological diseases could be found in 32/180 (17.8%) patients of ILI group, 21/127 (16.5%) of the influenza A group, and 19/90 (21.1%) of the influenza B group ($p=0.680$).

	influenza-like illness	influenza A	influenza B	p-value
liver disease	32/181 (17.7%)	7/127 (5.5%)	5/90 (5.6%)	<0.001
cardiac insufficiency	25/181 (13.8%)	7/127 (5.5%)	3/90 (3.3%)	0.005
arterial Hypertension	71/181 (39.2%)	36/127 (28.3%)	45/90 (50.0%)	0.005
pregnancy	6/181 (3.3%)	12/127 (9.4%)	1/90 (1.1%)	0.008
chronic renal failure	35/181 (19.3%)	12/127 (9.4%)	13/90 (15.1%)	0.057
coronary heart disease	30/180 (16.7%)	13/127 (10.2%)	8/90 (8.9%)	0.112
asthma	12/181 (6.6%)	11/127 (8.7%)	2/90 (2.2%)	0.151
smoking	29/181 (16.0%)	18/127 (14.2%)	9/90 (10.0%)	0.406

Diabetes Mellitus	25/181 (13.8%)	12/127 (9.4%)	9/90 (10.0%)	0.435
COPD	19/181 (10.5%)	17/127 (13.4%)	14/90 (15.6%)	0.469
malignancies	17/181 (9.4%)	13/127 (10.2%)	12/90 (13.3%)	0.604
neurological diseases	32/180 (17.8%)	21/127 (16.5%)	19/90 (21.1%)	0.680

Table 7 Past medical history including patients ≥ 18 years

3.10 Physical examination

At the physical examination 17/298 (5.7%) of the patients in the ILI-group presented with wheezing compared to 31/246 (12.6%) patients of the influenza A group, which showed a statistically significant higher amount. In the influenza B group 8/88 (9.1%) patients presented with wheezing (p=0.061). No significant difference could be found between the groups at the presentation of crackles. With 67/298 (22.5%) cases for the ILI-group, 47/245 (19.1%) for the influenza A group and 25/88 (28.4%) for the influenza B group (p=0.187).

	influenza-like illness	influenza A	influenza B	p-value
wheezing	17/298 (5.7%)	31/246 (12.6%)	8/88 (9.1%)	0.061
crackles	67/298 (22.5%)	47/246 (19.1%)	25/88 (28.4%)	0.187

Table 8 physical examination including all patients

3.10.1 Physical examination for adult-patients ≥ 18 years

At physical examination of the adult patients 7/181 (3.9%) of the patients in the ILI group presented with wheezing compared to 19/129 (14.7%) patients of the influenza A group, showing a statistically significant higher number. In the influenza B group 8/88 (9.1%) patients presented with wheezing (p=0.003). With 47/181 (26.0%) cases for the ILI group, 37/129 (28.7%) cases for the influenza A group, and 25/88 (28.4%) for the influenza B group no significant difference could be found between the groups for the clinical sign of crackles (p=0.504).

	influenza-like illness	influenza A	influenza B	p-value
wheezing	7/181 (3.9%)	19/129 (14.7%)	8/88 (9.1%)	0.003
crackles	47/181 (26.0%)	37/129 (28.7%)	25/88 (28.4%)	0.504

Table 9 Physical examination for adult patients ≥ 18 years

3.11 Vital parameters

For the vital parameters, again only the adult patients were looked at due to the demographic distribution.

The mean heart rate of the patient groups showed a statistically significant difference at first clinical presentation (p=0.006). With the mean amount of 101.17 bpm the influenza A group (range 60-207) showed a significant higher mean amount of bpm compared to the other groups. The ILI-group showed a mean heart rate of 96.61 bpm (range 51-200) and the influenza B group showed the lowest mean heart rate with 91.44 bpm (range 53– 139).

At first clinical presentation no statistically significant difference could be found in terms of mean systolic blood pressure (p=0.933) and mean diastolic blood pressure (p=0.916). Mean systolic blood pressure was 129.49mmHG for the Ili-group, 128.37mmHG for the Influenza A group and 129.21mmHG for the influenza B group. The mean diastolic Blood pressure was 77.34mmHg for the Ili-group, 76.81mmHG for the influenza A group and 76.61mmHg for the influenza B group.

	influenza-like illness	influenza A	influenza B	p-value
heart Rate bpm/Mean	96.61	101.17	91.44	0.006
blood pressure systolic	129.49	128.37	129.21	0.933
blood pressure diastolic	77.34	76.81	76.61	0.916

Table 10 Vital parameters of adult patients ≥ 18 years

3.12 Laboratory values

A significant difference in laboratory values between the 3 groups could be found regarding leukocytes, thrombocytes, eosinophils, monocytes, C-reactive protein, ALT, creatine kinase and lactate dehydrogenase. A detailed overview can be found in table 11 below.

3.12.1.1 Leucocytes

The Median number of Leucocytes showed a significant difference between the 3 groups ($p<0.001$). Influenza-like illness showed the highest median amount with 9.90 (G/l) compared to the influenza A group with 6.71 (G/l) and the influenza B group with 6.45 (G/l).

3.12.1.2 Thrombocytes

A significant difference could be found in regard to the median thrombocyte count ($p < 0.001$). With the median amount of 232 (G/l) influenza-like illness showed the highest amount, compared to the median amount of 214 (G/L) from influenza A and 178.5 (G/l) from the influenza B group. The direct comparison between the influenza A and influenza B group also showed a statistically significant difference ($p<0.001$).

3.12.1.3 Eosinophils

A significant statistical difference could be found in regard of the median amount of eosinophiles ($p=0.007$), with a significant higher amount in the influenza-like illness group. Due to the small numbers of the median, the mean values have been added in brackets at the bottom of the overview table for better understanding.

3.12.1.4 Monocytes

The Median number of Monocytes was significant higher in the influenza B group (11.0 %) compared to influenza A (9.1 %) and the influenza-like illness group (8.0%) ($p<0.001$).

3.12.1.5 C-reactive protein

All 3 groups showed an elevated Median amount of C-reactive protein compared to the standard values. In the direct comparison between the groups influenza-like illness showed a significant higher median amount (41.7mg/l) compared to the influenza A (19.2mg/l) and the influenza B (26.2mg/l) group ($p<0.001$).

3.12.1.6 Creatine kinase

A statistically significant difference could be found in regard to the median amount of creatine kinase levels. The influenza-like illness group showed the least median amount with 73.0 U/l compared to the influenza A group with 131.0 U/l and the influenza B group with 107 U/L (p=0.007).

3.12.1.7 Lactate dehydrogenase

Looking at the median amount of lactate dehydrogenase, a significant difference could be found (p=0.005). Influenza-like illness showed the least amount with 219 U/l compared to the influenza A group with 224.0 U/l. The influenza B group had the highest median value with 261.0 U/L.

3.12.1.8 Other laboratory values

No statistically significant differences could be found in the analyses of other laboratory values such as neutrophils, lymphocytes, creatinine, GGT and ALT.

median	influenza-like illness	influenza A	influenza B	p-value
leucocytes (G/l)	9.90	6.71	6.45	<0.001
thromocytes (G/l)	232	214	178.50	<0.001
monocytes (%)	8.0	9.1	11.0	<0.001
CRP (mg/l)	41.7	19.2	26.6	<0.001
ALT (U/l)	22.0	20.0	23.0	<0.001
LDH (U/l)	219.0	224.0	261.0	0.005
CK (U/l)	73.0	131.0	107.0	0.007
eosinophils (G/l) (median/mean)	0.18 (1,01)	0 (0.67)	0 (0.84)	0.007
creatinine (mg/dl)	0.87	0.94	1.04	0.122
neutrophils (%)	74.0	74.5	72.0	0.247

GGT (U/l)	30.0	26.0	29.0	0.396
lymphocytes (%)	14.8	15.0	16.0	0.816
AST (U/l)	29.0	31.0	33.5	0.858

Table 11 Laboratory values including all patients

3.12.2 Laboratory values for adult-patients older than 18 years

A significant difference in Laboratory Values between the 3 groups in regard to adult patients only, could be found regarding leukocytes, thrombocytes, neutrocytes eosinophiles, monocytes, C-reactive Protein, ALT, Creatine Kinase and Lactate dehydrogenase. A detailed overview can be found in table 12 below.

3.12.2.1 Thrombocytes for adult patients ≥ 18 years

Like the median number of Leucocytes, a significant difference could be found in regard to the median thrombocyte count ($p<0.001$). With the median amount of 219.5 (G/l) Influenza-like illness showed the highest amount, compared to the median amount of 186 (G/l) from influenza A and 178.5 (G/l) from the influenza B group.

3.12.2.2 Monocytes for adult patients ≥ 18 years

The median number of monocytes was significant higher in the influenza B group (11.0 %) compared to influenza A (9.0 %) and the influenza-like illness group (8.0%) ($p<0.001$).

3.12.2.3 C-reactive protein for adult patients ≥ 18 years

All 3 groups showed an elevated median amount of c-reactive protein compared to the standard values. In the direct comparison between the groups influenza-like illness showed a significant higher median amount (67.5mg/l) compared to the influenza A (33.0mg/l) and the influenza B (26.2mg/l) group ($p<0.001$).

3.12.2.4 Lactate dehydrogenase for adult patients ≥ 18 years

Looking at the Median amount of lactate dehydrogenase, a significant difference could be found. Influenza-like illness showed the least amount with 213 U/l compared to the

influenza A group with 221.0 U/l. The influenza B group had the median highest value with 261.0 U/L (p= 0.010).

3.12.2.5 Neutrocytes for adult patients ≥ 18 years

The Ili group showed a mean number of 76.3 (G/l) neutrocytes compared to the influenza A group with a mean number of 77 (G/l) which had the highest amount among the groups. The influenza B group showed the lowest mean number of 72.0 (G/l). Overall a statistically significant difference could be found (p=0.015).

3.12.2.6 Creatine kinase for adult patients ≥ 18 years

A statistically significant difference could be found in regard to the median amount of creatine kinase levels. The influenza-like illness group showed the least median amount with 77.0 U/l compared to the influenza A group with 142.0 U/l and the influenza B group with 107 U/L (p=0.026).

3.12.2.7 Eosinophiles for adult patients ≥ 18 years

A significant statistical difference could be found in regard of the median amount of eosinophils (p=0.031), with a significant higher amount in the Influenza-like illness group with a median amount of 0.175. Due to the small numbers of the median, the mean values have been added in brackets at the bottom of the overview table for better understanding.

3.12.2.8 Leucocytes for adult patients ≥ 18 years

The Median number of Leucocytes showed a significant difference between the 3 groups (p=0.039). Influenza-like illness showed the highest Median amount with 9.59 (G/l) compared to the influenza A group with 6.60 (G/l) and the influenza B group with 6.45 (G/l).

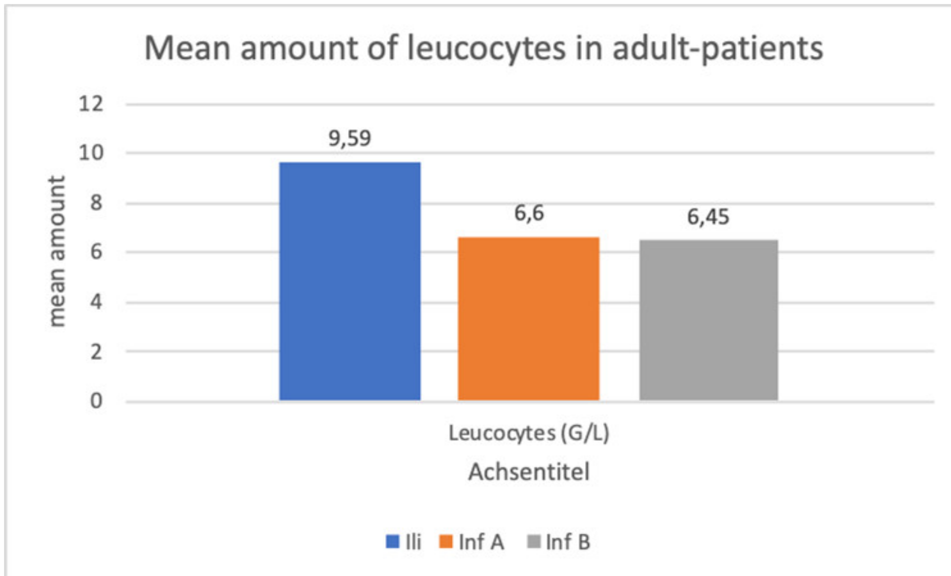


Figure 15 Mean number of leucocytes in adult patients ≥ 18 years

3.12.2.9 Other laboratory values for adult patients ≥ 18 years

No statistically significant differences could be found in the analyses of other laboratory values such as lymphocytes (p=0.088), ALT (p=0.097), GGT (p=0.143), creatinine (p=0.225), AST (p=0.906).

median	influenza-like illness	influenza A	influenza B	p-value
thrombocytes (G/l)	219.5	186	178.50	<0.001
monocytes (%)	8.0	9.0	11.0	<0.001
CRP (mg/l)	67.5	33	26.6	<0.001
LDH (U/l)	213.0	221.0	261.0	0.010
neutrophils (%)	76.3	77	72.0	0.015
CK (U/l)	77.0	142.0	107.0	0.026
eosinophils (G/l)	0.175 (0.95)	0 (0.51)	0 (0.84)	0.031

(median/mean)				
leucocytes (G/l)	9.59	6.60	6.45	0.039
lymphocytes (%)	12.0	12.0	16.0	0.088
ALT (U/l)	26.0	23.0	23.0	0.097
GGT (U/l)	39.0	34.0	29.0	0.143
creatinine (mg/dl)	1.01	1.00	1.04	0.225
AST (U/l)	27.0	30.0	33.5	0.906

Table 12 Laboratory values for adult-patients ≥ 18 years

4 Discussion

In this scientific thesis, data from patients with either influenza-like illness, influenza A or influenza B infection were retrospectively analysed. We analysed our data for demographics, hospitalization, outcome, medical imaging, clinical presentation, pre-existing medical conditions, physical examination, vital parameters and laboratory values. Finally, the data were compared between ILI and influenza, and between influenza A and influenza B. Aim was to evaluate differences or consistent patterns of the different diseases. Unless otherwise mentioned, the discussion focusses on the results regarding adult patients (older than 18 years).

First, in adults we observed a significant age difference between the ILI group and the influenza-subtypes (p=0.04). We observed the lowest mean age in H1N1 patients (43.5 years), associated with the H1N1 pandemic starting in 2009. This observation supports the results from an Austrian multicentre Study from 2009 (79) where 53.4% of the hospitalized adult H1N1 patients were between 18-28 years old, and only 11.5% were older than 64 years (79). Regarding mean age, the H1N1 group was followed by the ILI group (49.9 years). Patient with an H3N2 infection had a mean age of 53.8 years, and the influenza B group was significantly older than the other groups (65.3 years). In this context, pregnant patients were also more frequently seen in the influenza A group (9.4%) and less frequently in the ILI (3.3%) and rarely in the influenza B group (1.1%) (p=0.008). This can be explained by the high proportion of H1N1 patients, having the lowest age at onset of the disease of all groups. It is therefore particularly advisable for pregnant women to protect themselves with a vaccination (80). The low proportion of pregnant women in the influenza B group can be explained by the significant higher mean age and the small cohort. The fact that younger patients acquired H1N1 more frequently has several causes and has been widely discussed in the literature. The immune system of younger patients had less contact with similar influenza strains and therefore a lower pre-existing immunity to H1N1. Furthermore, the vaccination coverage is much lower in younger patients, which is why they showed less cross-immunity. Another hypothesis is that regardless of the pre-existing level of immunization, influenza A may be more immunogenic than influenza B and therefore causes more inflammation in immunocompetent individuals (81, 82).

The gender distribution in the adult ILI group and influenza B group was well-balanced (51% male vs 49% female and 50% male vs 50% female, respectively) but in the adult influenza A group males were somewhat overrepresented, however, without statistical difference (58% male vs 42% female, p=0.392).

Second, our data showed that adult patients infected with ILI had a higher probability for hospitalization compared to the influenza-subtypes (86% ILI vs 73% influenza A vs 64% influenza B, p<0.001). However, once hospitalised, patients suffering from influenza A we more likely to be transferred to and cared for in the ICU than patients with ILI or influenza B (7% ILI vs 13% influenza A vs 3 % influenza B, p<0.001).
The overall fatal outcome for all adult inpatients was 5.2% ILI vs 5.3% influenza A vs 3.4% influenza B (p=0.186). Adult influenza B patients were older and presumably more comorbid, but nonetheless had a lower hospitalisation rate, a lower ICU admission rate and a lower in-hospital mortality than the younger influenza A group. It is also possible, that very old influenza B patients were more frequently regarded as palliative cases, and therefore not hospitalized or not admitted to the ICU. However, the very low hospital mortality of the influenza B group does not support such a scenario.
Our hospitalisation and in-hospital mortality data are consistent with the results from other studies (25, 85), where influenza A was found to cause a more severe disease and more severe complications than influenza B.
The newer H1N1 virus strain of the influenza A in 2009/2010 had a high pathogenicity, and the lack of immunisation of the younger population might explain the higher rate of patients in the ICU. Interestingly patients of the influenza B group had the highest ICU-mortality rate (61% ILI vs 29% influenza A vs 67% influenza B). This seems somewhat high in comparison to literature data and is probably due to the small number of 3 patients with severe influenza B transferred to the ICU (83, 84).

Third, we analysed for signs and symptoms at the first clinical presentation. In terms of fever, the influenza B positive group was found to have a lower likelihood of elevated temperature (74% ILI vs 75% influenza A vs 50% influenza B, p<0.001). This is probably due to the higher average age compared to the other groups, causing a weaker immune response and thus a reduced temperature elevation, or less severe disease. Another reason might be a weaker immune response to the influenza B virus, compared to the influenza A infection.

Regarding the sign cough, a clear difference was found for patients who were infected with one of the influenza virus strains (46% ILI vs 77 % influenza A vs 63% influenza B, p<0.001).
Patients infected with influenza B had a significantly lower chance of showing headache as a clinical symptom (8.9% Inf B vs 22 %ILI vs 32% Inf A, p<0.001). It is therefore safe to assume that, if a patient presents to the outpatient clinic with influenza-like signs and symptoms but without headache, it is most likely not an influenza B infection.
The clinical symptom of fatigue was particularly frequent in patients who had influenza A (50%). Compared to the other two groups, fatigue was twice as frequent in the influenza A group as in the ILI group (25%), and threefold as high as in the influenza B group (16%, p<0.001), which is mainly due to the specificities of the influenza A virus, and especially of the H1N1 subgroup.
In summary, adult influenza B patients presented with a milder clinical picture (less fever, less cough, less headache, less fatigue) than patients with influenza A.
In terms of medical imaging, no significant difference could be observed in the number of chest X-rays ordered (82% ILI vs 82% influenza A vs 82% influenza B, p=0.959). However, a difference could be observed with respect to new infiltrates (38% ILI vs 35% influenza A vs 23% influenza B, p=0.048). In contrast, there was a significant difference in the amount of ordered CT´s of the thorax (22% ILI vs 14% influenza A vs 9% influenza B, p=0.019), and new infiltrates (54% Ili vs 78% influenza A vs 25% influenza B). The probability for pulmonary infiltrates as a correlate for a viral pneumonia was lower in influenza B than in the influenza A group. The high rate of pulmonary infiltrates in the ILI group might indicate, that many of the ILI patients actually had a community acquired pneumonia (CAP).

Regarding pre-existing conditions, we were able to show that there is no significant relationship between lung diseases such as bronchial asthma (7% ILI vs 9% influenza A vs 2% influenza B, p=0.151), COPD (11% Ili vs 13% influenza A vs 16% influenza B, p=0.469) that would promote an infection with ILI or influenza A or B. In our study, we did not evaluate how pre-existing medical conditions affected outcome of the patients.

Heart diseases such as coronary heart disease (17% ILI vs 10% influenza A vs 9% influenza B, p=0.112) and cardiac insufficiency (14% ILI vs 6% influenza A vs 3% influenza B, p=0.005) were found more frequently in the ILI group. Patients with arterial

hypertension were more likely to be infected with influenza B (28% ILI vs 39% influenza A vs 50% influenza B, p=0.005). The high number in the influenza B group can be explained by the high average age of the group. It is therefore particularly advisable for patients of advanced age to protect themselves with the 4-strain influenza vaccine. (86)
For patients with chronic renal insufficiency (p=0.057), diabetes mellitus (p=0.435), malignancies (p=0.604) or neurological disease/s (p=0.680), no significant relation to the infections could be drawn. For diabetes mellitus, no sub-analysis was performed with regard to type.

In the clinical examination of the patients, we found that more patients in the influenza A group initially showed the clinical sign of wheezing (4% ILI vs 15% influenza A vs 9% influenza B, p=0.003). No difference could be found for crackles (26% ILI vs 29% influenza A vs 29% influenza B, p=0.504).
In terms of vital signs, we found a significant difference in mean heart rate/bpm (96 ILI vs 101 influenza A vs 91 influenza B bpm, p=0.006). This can be explained by the age gradient in our groups. Younger patients, who were mainly infected with influenza A, have a more intense immune response and higher fever than older patients. Furthermore, one has to consider that older patients are frequently on medication, e.g., beta blockers, which decrease a strong elevation of the heart rate. No significant difference could be found for systolic (p=0.933) and diastolic (p=0.916) blood pressure.
No difference in height and weight was found to determine the likelihood of the disease. This also applies to BMI. It is nevertheless advisable to keep your body weight in a normal range.

A special focus was placed on the inflammatory parameters in the analyses of laboratory values. In the analysis of the median leukocytes count, we were able to reproduce the results of a previous thesis. It was found that patients who suffered from one of the influenza viruses were more likely to have a relative leukocytopenia (9.59 G/l ILI vs 6.60 G/l influenza A vs 6.45 G/l influenza B, p=0.039). Furthermore, we could evaluate a difference in the mean level of CRP (67 mg/l ILI vs 33 mg/l influenza A vs 26 mg/l influenza B, p<0.001). In addition to the higher rate of pulmonary infiltrates in the ILI group, the higher CRP level and the higher median leukocyte count of the ILI group again indicates, that a relevant part of the ILI group might have suffered from a bacterial CAP.

The mean number of absolute monocytes was increased in influenza B (8% ILI vs 9% influenza A vs 11% influenza B, $p<0.001$)
This could provide a laboratory tool to help distinguish these different disease entities. Yet, a more detailed and extended investigation would be needed here.
We were also able to detect significant laboratory differences for CK ($p=0.026$) and LDH ($p=0.010$). However, since these parameters have little significance overall and can also be increased or decreased in case of various other diseases, we did not discuss them here. Differences in eosinophil counts ($p=0.031$) are also not discussed in detail here, as they do not play a decisive role clinically and are not differentiated enough in the routine laboratory analysis.

4.1 Limitations

The main limitation is the retrospective study design. At the time of diagnosis and treatment, it was not planned to conduct a study or to draw statistical significance from routinely collected data. Although most of the data were collected at first presentation of the patient, the study is nevertheless subject to bias. Other limitations are that the case groups have different ages, and that a non-uniform test method was chosen to determine the disease. Another major limitation is the local restriction to hospitals in Styria. It is also important to mention that we do not have any long-term data, especially on the outcome of outpatients. Although one may assume that a hospital consultation will take place in the case of more severe courses, we cannot evaluate the exact number of such consultations.

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