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ACUTE RESPIRATORY ILLNESS AND RESPIRATORY VIRUSES – ASSOCIATIONS TO OLDER CITIZENS' STATE OF HEALTH

Matti Aronen

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To my beautiful family

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MATTI ARONEN: Acute respiratory illness and respiratory viruses – Associations to older citizens' state of health
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ABSTRACT

The role of many respiratory virus infections among older individuals remains unclear. Respiratory virus detection provides prognostic information about asthma development in children suffering from severe lower airway illnesses, but respective reports in older adults are scarce. Increased susceptibility to respiratory tract infections among older people is thought to be interlinked with poor vitamin D status, nourishment, and general immunological state.

Our aim was to investigate the virus presence in the nasopharynx in those over 65 by modern methods and evaluate associations between virus findings and the severity of respiratory illness and chronic illnesses. In addition, we studied whether viral pathogens and conventional inflammatory markers correlate to the presence, signs and symptoms, or prognosis of pneumonia among these patients. Furthermore, we investigated whether serum 25(OH)D, albumin, and LL-37 levels could have prognostic value in older patients with acute respiratory infection.

Virus detection was more common among older patients with respiratory symptoms than those without. Over 100 mg/L CRP values with respiratory symptoms were associated with death during hospital stays. Respiratory virus detections did not correlate with clinical course of pneumonia episodes among those studied. Presence of a respiratory virus was associated with fewer revisits among episodes with respiratory symptoms. Serum 25(OH)D deficiency and hypoalbuminemia were present in more than 50% of the study patients. Low serum albumin level was associated with more severe disease; longer hospital stay; death at ward; and 1-, 2- and 5-year mortality. On the contrary, no associations were seen between serum 25(OH)D or LL-37 levels with disease severity, short-term clinical outcome or long-term survival.

The results indicate that the presence of respiratory viruses in the upper airways is only modestly associated with respiratory symptoms among older patients. Moreover, respiratory virus detection does not seem to be linked to pneumonia or more severe clinical course of disease. Thus, pneumonia should be treated as a bacterial disease regardless of the virus finding and our data do not support routine virus diagnostics for older patients with pneumonia. Serum albumin level may provide valuable information about the patients' general health and the recovery potential in treating older patients with respiratory symptoms.

KEYWORDS: Respiratory tract virus, older patients, pneumonia, albumin

TURUN YLIOPISTO
Lääketieteellinen tiedekunta
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TIIVISTELMÄ

Useiden hengitystievirusinfektioiden merkitys ikääntyneillä on osin epäselvä. Vaikeaa alahengitystieinfektiota sairastavilla lapsilla hengitystieviruksen tunnistaminen antaa ennusteellista arvoa, mutta vastaavaa tutkimusta on vanhusväestöstä vähän. Vanhenevan inhmisen lisääntyvän alttiuden hengitystieinfektioille on ajateltu liittyvän mm. D-vitamiinin saantiin, ravitsemukseen ja yleiseen immunologiseen tilaan.

Tavoitteenamme oli selvittää moderneilla menetelmillä, mitä viruksia ikääntyneillä, yli 65-vuotialla, nenänielusta löytyy ja arvioida yhteyttä näiden löydösten ja hengitystiesairauden vaikeuden ja kroonisten hengitystiesairauksien välillä. Tutkimme, korreloivatko viruslöydökset ja perinteiset tulehdusparametrit keuhkokuumelöydöksiin, keuhkokuumeen oireisiin tai ennusteeseen ikääntyneillä. Lisäksi selvitimme, voisiko seerumin 25(OH)D-, albumiini-, ja LL-37-pitoisuuksilla olla ennusteellista arvoa akuuttia hengitystieinfektiota sairastavilla vanhuksilla.

Vanhukselta, jolla oli hengitystieoireita, löydettiin useammin hengitystievirus kuin oireettomalta verrokilta. Yli 100 mg/l CRP-arvot hengitystieoireisella vanhuksella kytkeytyi kuolemaan osastohoidon aikana. Hengitystieviruslöydökset eivät kytkeytyneet keuhkokuumeen taudinkulkuun vanhuksilla. Hengitystieviruksen löytäminen ennusti harvempaa uusintakäyntimäärää hengitystieoireisilla. Seerumin 25(OH)D-puutosta ja hypoalbuminemiaa tavattiin molempia yli puolella tutkimuspotilaista. Alhainen seerumin albumiinipitoisuus kytkeytyi vaikeampaan taudinkuvaan, pidempiin hoitojaksoihin, osastohoidonaikaiseen kuolemaan sekä yhden, kahden ja viiden vuoden mortaliteettiin. Sitä vastoin, seerumin 25(OH)D- ja LL-37-pitoisuudet eivät kytkeytyneet taudin vaikeuteen, lyhyen ajan ennusteeseen tai pitkän ajan mortaliteettiin.

Tulokset osoittavat, että hengitystieviruslöydökset ylähengitysteissä ovat vain heikosti yhteydessä vanhojen potilaiden hengitystieoireisiin. Viruslöydökset eivät näytä ennustavan keuhkokuumeetta tai vaikeampaa taudinkuvaa. Vanhusten keuhkokuume pitäisikin hoitaa bakteeritautina viruslöydöksistä riippumatta eikä tutkimuksemme tue rutiininomaisten virusdiagnostiikkaa. Seerumin albumiinipitoisuus saattaa tarjota arvokasta tietoa hengitystieoireisen vanhuspotilaan yleisestä terveydentilasta ja toipumispotentiaalista.

AVAINSANAT: Hengitystievirus, vanhus, keuhkokuume, albumiini

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Abbreviations

ADL	Physical activity of daily living
BoV	Human bocavirus
COPD	Chronic obstructive pulmonary disease
CI	Confidence interval
CoV	Coronavirus
CRP	C-reactive protein
MMSE	Mini-Mental State Examination
MPV	Human metapneumovirus
RV	Rhinovirus
SD	Standard deviation
OR	Odds ratio
PIV	Parainfluenza virus
PCR	Polymerase chain reaction
RSV	Respiratory syncytial virus
TIA	Transient ischemic attack
WBC	White blood cell count
25(OH)D	25-hydroxyvitamin D

List of Original Publications

This dissertation is based on the following original publications, which are referred to in the text by their Roman numerals:

I Aronen M, Viikari L, Vuorinen T, Langen H, Hämeenaho M, Sadeghi M, Söderlund-Venermo M, Viitanen M, Jartti T. Virus Etiology of Airway Illness in Elderly Adults. J Am Geriatr Soc. 2016 Jun;64(6):1358-60.

II Aronen M, Viikari L, Kohonen I, Vuorinen T, Hämeenaho M, Wuorela M, Sadeghi M, Söderlund-Venermo M, Viitanen M, Jartti T. Respiratory tract virus infections in the elderly with pneumonia. BMC Geriatr. 2019 Apr 16;19(1):111.

III Aronen M, Viikari L, Langen H, Kohonen I, Wuorela M, Vuorinen T, Söderlund-Venermo M, Viitanen M, Camargo CA Jr, Vahlberg T, Jartti T. The long-term prognostic value of serum 25(OH)D, albumin, and LL-37 levels in acute respiratory diseases among older adults. BMC Geriatr. 2022 Feb 21;22(1):146.

1 Introduction

The number of citizens over 80 is rising in Western societies due to safer environments and modern medicine. In Finland the most rapidly growing age groups are 80-84, 85-89 and 90 and above (Population projection, 2023). Still, the relevance of respiratory virus infections among this group with aging immune systems remains unclear. With an ever-growing share of older residents, virus infections causing acute illnesses may play even a more considerable role in the future. With the influenza virus test often being the only virus test used by physicians, the role of other respiratory viruses may be underestimated in cause-of-death records (Jartti et al., 2011). Virus diagnostics in older patients have not managed to reduce antibiotic use or the length of hospital stay much at all (Hernes et al., 2014, Semret et al., 2017). The development of molecular techniques during the last few decades have improved diagnostics of viral infections. Rapid antigen detection tests and polymerase chain reaction (PCR) diagnostics are more and more often available for respiratory virus detection (Talbot & Falsey, 2010). In addition, PCR-based methods are more sensitive than older methods for the diagnosis of many familiar respiratory virus infections, and multiplex PCR assays also give clinicians valuable information of viral coinfections (Talbot & Falsey, 2010, Jartti et al., 2008).

According to current knowledge, influenza virus (flu), respiratory syncytial virus (RSV) and parainfluenza virus (PIV) cause substantial respiratory morbidity and mortality in older patients (Treanor & Falsey, 1999, Thompson et al., 2003, van Asten et al., 2012). RSV infections often coincide, in the same cold winter months, with influenza epidemics, and therefore RSV's effect on mortality may be underestimated (Nicholson, 1996). In Finland, major peaks in RSV-related hospital admissions usually occur every second December (Waris, 1991). All-cause mortality rate associated with respiratory viral infection increases with age, and among over-85-year-old subjects, it is as high as approximately 6%–7% (van Asten et al., 2012). Underlying medical conditions and poor responses to influenza vaccine among older adults are risk factors for a severe respiratory viral infection (Yu et al., 2011, Jartti et al., 2011).

Respiratory tract infections and pneumonia cause most infectious deaths of older people in developed countries, and morbidity, mortality, and costs are high around

the world (Prina et al., 2015, Ruuskanen, 2011, Meyer, 2004). In one-third of lower respiratory tract infections among older patients, a respiratory virus can be implicated (Flamaing et al., 2003, Kobashi et al., 2001). In addition to influenza, RSV and PIV, other viral causes include rhinovirus (RV) and coronaviruses (CoV) (Ruuskanen, 2011). There are only a few reports about the usefulness of respiratory virus diagnostics, and the research has focused on pediatric patients. There is evidence that mixed infections in adults, especially rhinovirus with pneumococci, associate with more severe pneumonia (Jennings, 2008, Templeton et al., 2005, Johansson et al., 2011, Burk et al., 2016). There are no good methods available to differentiate sole bacterial, mixed, and sole virus pneumonias (Caglayan Serin et al., 2014, Pavia, 2013). The above-mentioned finding suggests that virus diagnostics among older patients could be clinically relevant.

Vitamin D receptors exist in most tissues and cells in the body, and multiple health benefits have been suggested for vitamin D (Holick et al., 2011). Strong associations between serum 25-hydroxyvitamin D (25(OH)D) deficiency and frailty have been shown (Wong & Flicker, 2015, Walston et al., 2006). Even all-cause mortality of ambulatory older people has been suggested to decrease with vitamin D supplementation, and associations between serum 25(OH)D concentration and respiratory disease morbidity have been shown (Bjelakovic et al., 2014, Kim et al., 2015, Holter et al., 2016, Quraishi et al., 2013, Monlezun et al., 2015).

Hypoalbuminemia is associated with worse recovery after acute pathologies among older patients (Cabrerizo et al., 2015, El-Solh et al., 2003). Serum albumin levels have been stated to reflect patients' inflammatory state (Soeters et al., 2019). Malnutrition is associated with poor clinical outcome in many diseases (Demir & Özbek, 2021, Shirakabe et al., 2018). Also, short-term mortality risk during hospital care associates with lowered serum albumin levels (Akirov et al., 2017, Hedlund, 1995, Liu et al., 2015). Special care for community-acquired pneumonia patients with low serum albumin levels has been suggested previously (Hedlund, 1995, Shirata et al., 2021).

After infection, LL-37 cathelecidin invites neutrophils, monocytes, dendritic and T cells to act and is released by epithelial cell and leukocytes (Bandurska et al., 2015). It can be found in the human lung, where it may have an antimicrobial effect (Bals et al., 1998). LL-37 has shown antiviral activity against RSV in vitro (Currie et al., 2013). Differences in serum LL-37 levels have been shown between bacterial pneumonia patients and healthy controls (Majewski et al., 2018). In a study of older sepsis patient, LL-37 was indicated to have predictive value in 28-day survival (Castañeda-Delgado et al., 2013, Guo et al., 2018). Thus far, clinical studies concerning serum LL-37 among older patients are scarce.

We set a hypothesis that serum 25(OH)D, albumin, and LL-37 levels of older patients hospitalized with respiratory symptoms have a positive association with

short- and long-term mortality. Our prospective cohort study investigated the long-term predictive value of serum 25(OH)D, albumin, and LL-37 levels by assessing 1-, 2- and 5-year survival. Our other hypothesis was that there is an association between respiratory virus detections and the presence of pneumonia and chronic illnesses and the severity of acute disease.

The study cohorts and samples for this thesis were gathered well before the COVID-19 pandemic, and this new virus and its variants have intentionally been excluded from this work.

2 Review of the Literature

2.1 Older patients with acute illness

Older patients are ever more common in primary care units due to increases in life expectancy. Common chronic diseases cumulate to older citizens, and overlapping comorbidities elevate the risk of acute illness ("Monisairas potilas," 2023). Reduced exercise tolerance and polypharmacy increase the risk further (Ellis et al., 2014). Geriatric patients with acute illness are usually brought to primary care units with severe symptoms. They may have fallen, suffer from dyspnea, have fever, or be confused, and there are many possible diagnoses of symptoms. Diagnostics are often challenging; anamnestic information may be scarce and even misleading, symptoms may vary in intensity and be different than with younger patients, and there may be many chronic illnesses behind changing the classical symptoms (Kemp et al., 2020). Pneumonia without fever or cough is a typical example of the altered clinical picture of a disease among older patients. (Tilvis, 2016)

Both susceptibility to infections and their severity increase with age. Two factors behind this are the age-related changes in immune system and chronic diseases, with the latter having a stronger correlation. Chronic disease-related risk factors for infectious diseases are, for example, impaired cough reflex, increased aspiration susceptibility, skin problems, and wounds, as well as falling, physical inactivity and circulatory failure-related traumas. Age-related changes in the immune system increase the incidence and severity of infections and impair vaccination response. (Sammalkorpi, 2016a)

2.2 Infectious respiratory tract diseases

Two the most significant infectious respiratory diseases among older individuals are influenza virus infection and pneumonia. Influenza virus causes epidemic intensity correlating excess mortality almost solely among over-65-year-olds. Vaccination against seasonal influenza virus reduces pneumonia incidence during influenza epidemics and is provided free of charge for over-65-year-olds in Finland. It is also

shown that vaccinating health care workers reduces mortality in inpatients. Pneumonia incidence and mortality increase with age in adults. In addition to age, male gender, chronic pulmonary diseases, alcoholism, immune deficiency, heart diseases and inpatient status have shown to be risk factors for pneumonia. Pneumonia symptoms among older people are often hard to detect; fever and respiratory symptoms are less common among older patients than among younger ones. (Sammalkorpi, 2016b) In Finland, vaccination against pneumococcal disease is recommended for over-65-year-olds, and it is estimated that about half of severe disease cases among 65- to 74-year-olds could be prevented with vaccination ("Yli 65-vuotiaiden pneumokokkirokotukset - THL," 2023). Any means of making pneumonia detection easier, or even alerting practitioners to patients' increased risk of pneumonia, would come into heavy use.

2.2.1 Upper respiratory tract infections

Upper respiratory tract infections are considered the common cold or flu, sinusitis, otitis (externa), pharyngitis, laryngitis, bronchitis and epiglottitis (Ruuskanen & Heikkinen, 2011). Here we focus on the common cold, even though symptoms and pathogens greatly overlap with other, often virus-caused, illnesses named above. Mild upper respiratory illness is conventionally called the common cold, and typical symptoms are nasal stuffiness and discharge, sneezing, sore throat and cough. Numerous viruses can cause the common cold, and it is usually a self-limited illness affecting the upper respiratory tract. (Heikkinen & Järvinen, 2003)

The development of PCR-based methods in virus diagnostics has increased the viral detection rate from clinical samples since the 1990s and also set new possibilities in virology regarding the common cold (Jartti et al., 2011, Heikkinen & Järvinen, 2003, Mäkelä et al., 1998). Virus etiology cannot be deduced from symptoms in the common cold. Even symptoms from influenza virus infection may vary from none to severe illness, and a mild streptococcal pharyngitis may be indistinguishable from the common cold. (Heikkinen & Järvinen, 2003)

2.2.2 Lower respiratory tract infections

Lower respiratory infections are the world's leading health problems. In developed countries, they cause morbidity and mortality, especially among patients with chronic conditions and older patients. Lower respiratory infections include bronchitis, pneumonia, empyema and lung abscess, of which pneumonia is our focus here. (Korppi & Järvinen, 2011a) Pneumonia is defined as infection of the lungs. It is most often a bacterial infection or a mixed infection having both virus and bacteria

present. In addition, pathogens may also be solely viral or even fungal in immunocompromised patients (Ottosen & Evans, 2014). The etiology of pneumonia cannot be reasoned from symptoms and clinical picture. Pneumonia occurs especially in young children and older people, and male gender is more susceptible. (Korppi & Järvinen, 2011b)

Pneumonia subtypes, community-acquired pneumonia, hospital-acquired pneumonia, ventilator-associated pneumonia and aspiration pneumonia may be difficult to distinguish from one another (Ottosen & Evans, 2014).

2.3 Respiratory infection-causing pathogens

Influenza is the most important virus disease among older people, being relatively common and causing many complications (Sammalkorpi, 2016b). Many micro-organisms are associated with pneumonia, and the highest mortality occurs in patients over 75 years old and in children under 5 (Ruuskanen, 2011). It has been shown that, in addition to the most common bacterial pathogens, in 13%–31% of lower respiratory infections in older patients, a respiratory virus is present (Talbot & Falsey, 2010). In a systematic review and meta-analysis, Shi et al. stated that RSV, influenza, PIV, human metapneumovirus (MPV), AdV, RV, and CoV are important acute respiratory disease-causing pathogen asmong older adults (Shi et al., 2020). In Table 1 are presented incidences of different pathogens reported in community-acquired pneumonia episodes in adult and older adult patients in the literature (Widmer et al., 2012, Liu et al., 2009, Lieberman, 2010, Pierangeli et al., 2011, Glezen et al., 2000, Falsey et al., 2002, Thiberville et al., 2012, Atmar et al., 2012, Ren et al., 2011, Khadadah et al., 2010, Ren et al., 2009, Johnstone et al., 2008, Minosse et al., 2008, Kaye et al., 2006, Saito et al., 2006, Mermond, 2010, Cao, 2010, Köksal, 2010, Nicholson et al., 1997, Lieberman et al., 2003, Falsey et al., 2005). Still, the role of respiratory viruses in pneumonia episodes is still unclear. Moreover, it is still not clear if detected respiratory viruses among older patients subject to pneumonia and if so, whether there are differences in this feature between different respiratory viruses.

Table 1. Incidence rates of different pathogens reported in community-acquired pneumonia episodes in adult and older adult patients in the literature.

			DIAGNOSTIC METHODS USED					BACTERIA				RESPIRATORY VIRUSES							
STUDY	**n**	**Age (y)**	**Culture**	**Antigen**	**Serology**	**PCR**	**Virus positives of all with pneumonia (%)**	**M. pneumoniae**	**S. Pneumoniae**	**H.influenzae**	**C. Pneumoniae**	**CoV**	**MPV**	**Influenza**	**AdV**	**RSV**	**Enterovirus**	**RV**	**Parainfluenza**
KHADADAH ET AL. 2010	1014	3d–76				+	28					0		3	4	10		10	1
LIU ET AL. 2009	610	mean 52	+		+		19	21	10	9				9	9	4			
FALSEY ET AL. 2005	608	≥65	+		+	+								5		8			
REN ET AL. 2011	607	>65				+						4							
MINOSSE ET AL. 2008	510	mean 56	+		+							3	0		1	0		33	
WIDMER ET AL. 2012	508	≥50				+							5	6		6			
NICHOLSON ET AL. 1997	497	60–90	+	+		+	42	0			1	12		4	0	3		24	1
REN ET AL. 2009	456	>66				+						4	1	15	0	2	2	6	6
KAYE ET AL. 2006	435	>65				+							5			5			
THIBERVILLE ET AL. 2012	286	mean 31				+						3	1		1		2	20	3

SAITO ET AL. 2006	232	mean 60				+	16	5	25	19	7								
KÖKSAL 2010	218	mean 57.5	+	+	+		33	22	23	10				7		16			8
CAO 2010	197	mean 32.5	+	+		+	28	63	8	1		1	2		5	2		2	
JOHNSTONE ET AL. 2008	193	median 71	+		+	+	15	2	7	1	2	2	4	4	1	3		2	2
LIEBERMAN 2010	183	mean 59.5				+	32					13	1	4	2	7		5	
GLEZEN ET AL. 2000	150	>65	+	+	+		17					1		5	0	1	1	2	6
PIERANGELI ET AL. 2011	143	>65				+	30						1			3		15	
MERMOND 2010	137	>16	+	+	+	+	21	5	41	10									
LIEBERMAN ET AL. 2003	133	>65			+		39	11	18	2	2			13	5	5			17
FALSEY ET AL. 2002	100	>65			+	+	12					8						4	
ATMAR ET AL. 2012	62	>65	+			+	26					3	3	6	0	3	0	5	
					Average		**24**	**16**	**19**	**7**	**3**	**5**	**2**	**7**	**2**	**5**	**1**	**11**	**5**

PCR, polymerase chain reaction; CoV, coronavirus; MPV, human metapneumovirus; ADV, adenovirus; RSV, respiratory syncytial virus; RV, rhinovirus

2.3.1 Viral pathogens

Rhinovirus is the most common respiratory pathogen in all age groups, causing 50%–80% of all common colds (Jartti et al., 2011, Jartti et al., 2012, Jacobs et al., 2013). Human rhinovirus belongs to the family *Picornaviridae* and has single-stranded positive-sense RNA genome (To et al., 2017). They are the most prevalent human respiratory viruses, with over 100 different serotypes classified into three subgroups: A, B, C and even a fourth subgroup D have been suggested (Jartti et al., 2011, To et al., 2017, Lee et al., 2007, Palmenberg et al., 2009). Rhinovirus typically causes a mild upper respiratory disease year-round, and epidemics peak typically in fall and spring, before and after influenza and RSV epidemics (Jartti et al., 2011, Kodama et al., 2017). However, severe rhinovirus outbreaks among older people, with high mortality and morbidity comparable to influenza virus, have been reported in long-term care facilities, nursing homes and hospitals. Rhinovirus may cause morbidity (up to 100%) and mortality (up to 21%) in long-term care facilities (Louie et al., 2005). The morbidity and mortality in these outbreaks may result from residents' susceptibility to secondary bacterial infections. (Louie et al., 2005, Hung et al., 2017, Hicks et al., 2006, Wald et al., 1995) Studies in patients with asthma and COPD have shown that rhinovirus can trigger inflammatory reaction in the lower airways and exacerbate these chronic lung diseases. (To et al., 2017) However, the role of rhinovirus infections among older patients remains unclear, and information is scarce. (Jartti et al., 2011, Piralla et al., 2009) Whether hospital episodes caused by all common rhinovirus infections could even serve as prognostic tool in assessing older patients' general condition is unclear. No vaccination or other treatment against rhinovirus infection available.

Influenza virus is an RNA virus belonging to the *Orthomyxoviridae* family. There are four types of these viruses, influenza A, B, C and D of which only A and B cause clinically important disease in humans. (Ghebrehewet et al., 2016) Influenza virus can cause an illness ranging from mild to life-threatening. The World Health Organization estimates that seasonal influenza results in 3 to 5 million cases of severe illness and 290,000–650,000 respiratory deaths annually (World Health Organization, 2018). Influenza A most commonly causes epidemics, but influenza viruses can even cause pandemics due to antigenic alterations (Uhnoo et al., 2003). Influenza viruses can cause severe respiratory disease in all age groups, but there is ongoing debate about the benefits of influenza vaccination in older adults (Talbot et al., 2012, Simonsen et al., 2007,

Clark & Lynch, 2011). There is no direct evidence from placebo-controlled randomized trials available on the effectiveness of vaccines among older patients, due to ethical and scientific reasons (Verhees et al., 2018). In contrast to the seasonal influenza, the most severe epidemics, usually caused by influenza A virus, hit children and young adults worst because older people are often protected by antibodies from previous illnesses (Jartti et al., 2011, Centers for Disease Control and Prevention [CDC], 2010, Fowlkes et al., 2011). Fowlkes et al. reported that during the influenza A (H1N1) epidemic in 2009 in the U.S., only 14% of influenza-related deaths occurred in the age group 65 and older while the vast majority, 69%, were in the 25–64 age group (Fowlkes et al., 2011). Vaccination against seasonal influenza is recommended to older people because underlying medical conditions make them more susceptible to influenza-related complications and death (Thompson et al. 2003, Uhnoo et al., 2003, Clark & Lynch, 2011, Elliot & Fleming, 2008).

Respiratory syncytial virus is a single-stranded, negative-sense RNA virus that belongs to the *Pneumoviridae* family (Kodama et al., 2017, Haber, 2018, Collins et al., 2013). Two major antigenic groups, A and B, have been recognized, and outbreaks peak in December or January in temperate-climate countries (Haber, 2018, Borchers et al., 2013). Respiratory syncytial virus may cause clinical disease, manifesting from asymptomatic or mild cold symptoms to pneumonia, respiratory failure, and death (Kodama et al., 2017, Walsh et al., 2007). Among older and high-risk adults, RSV may cause disease burden similar to seasonal influenza (Falsey et al., 2005, Haber, 2018). Although there are some differences in symptoms caused by RSV as compared to influenza virus, clinical differentiation one from another is not possible, which is inconvenient because epidemics often partially overlap (Walsh et al., 2007). Falsey et al. reported in their study that patients hospitalized as having either influenza A or RSV infection suffered from equally severe disease when evaluated on the basis of the length of their hospital stay, whether the patient had pneumonia, whether they needed intensive care or mechanical ventilation, and mortality (Falsey et al., 2005). Severe outbreaks have been described in geriatric hospitals, senior care facilities, and nursing homes since the 1970s (British Medical Journal [Clinical research ed.], 1983, Hart, 1984, Sorvillo et al., 1984). There is some evidence that higher loads of RSV and increased interleukin 6 levels are associated with more severe disease in RSV infections (Kodama et al., 2017). Pro-inflammatory cytokine interleukin 6 level elevation has been associated with physical function decline and chronic diseases, typical of older patients (Kodama et al., 2017, Maggio et al., 2006). Immunosenescence may elevate older patients's risk of having symptomatic RSV infection via reduced antibody titers in serum. For preterm

infants and high-risk children, there is a monoclonal antibody available, and the first vaccine against RSV was approved by the U.S. Food & Drug Administration in May 2023 (Kodama et al., 2017, Falsey & Walsh, 1998, Villafana et al., 2017, U.S. Food & Drug administration, 2023).

Human parainfluenza virus belongs to the *Paramyxoviridae* family and is a negative-sense RNA virus. There are four major serotypes of parainfluenza virus, 1–4, and their seasonal trends differ. (Kodama et al., 2017, Fry et al., 2006) Interestingly, in the U.S. Fry et al. reported that parainfluenza 1 seems to peak during September–December during odd-numbered years and that parainfluenza 3 occurrence may be linked to this during even-numbered years (Fry et al., 2006). Parainfluenza viruses 1–3 can cause upper and lower respiratory tract disease, especially in children, and usually cause only a mild upper respiratory disease in adults. However, the risk of severe parainfluenza infection is raised among older patients again. Less is known about parainfluenza virus 4, which seems to be rarely isolated. Parainfluenza types 1–3 each have a strong relationship to specific clinical syndromes, age of child, and time of year. However, among adults, symptoms overlap greatly with other respiratory illnesses, and asymptomatic infections have also been documented. (Liu et al., 2013, Henrickson, 2003, Russell & Ison, 2017) There are several reports describing parainfluenza outbreaks in long-term care facilities with older residents, and parainfluenza virus infection is suspected of predisposing patients to pneumonia (Parainfluenza infections in the elderly 1976-82, 1983, Fiore et al., 1998). There is no effective antiviral therapy or vaccination available for parainfluenza virus infection (Russell & Ison, 2017, Branche & Falsey, 2016).

Human coronavirus belongs to the *Coronaviridae* family and is a positive-stranded RNA virus. Coronaviruses are a large and diverse group of viruses usually causing only a mild self-limiting upper respiratory disease but have also caused severe epidemics and even pandemics; severe acute respiratory syndrome (SARS) in 2003, Middle East respiratory syndrome (MERS) in 2012, and the recent SARS-CoV-2 (COVID-19) pandemic in 2019. (Wevers & van der Hoek, 2009, Almaghrabi & Omrani, 2017, Peeling et al., 2022) Coronaviruses are detected in from 1%–10% of people of all ages with acute respiratory tract infections (Pyrc et al., 2007). The most common serotypes causing respiratory diseases appear to be human coronavirus OC43 and 229E causing the common cold (Kodama et al., 2017, Wevers & van der Hoek, 2009). Since the SARS epidemic, in addition to SARS-CoV-2, two new coronaviruses have been identified – human coronavirus NL63 and HKU1 – and later found throughout the world. They are associated with usually mild upper respiratory diseases but can also cause more severe clinical symptoms among young children, older people,

and those with compromised immunological state. (Pyrc et al., 2007, van der Hoek et al., 2004, Woo et al., 2005) Coronaviruses have also caused severe outbreaks among older people living in long-term care facilities. Patrick et al. described a coronavirus OC43 outbreak with 67% attack rate and 8% mortality in a frail population. SARS coronavirus was first suspected there because of the severity of the outbreak and serological cross-reactivity between SARS and OC43. (Patrick et al., 2006, Falsey et al., 2008) Birch et al. described outbreaks of coronavirus OC43 in three different and geographically unrelated long-term care facilities (Birch et al., 2005). Outbreaks were mistaken as influenza outbreaks at fist by epidemiological and clinical data. However, reverse transcriptase-polymerase chain reaction (RT-PCR) confirmed infections as coronavirus OC43 infections while no other respiratory viruses were detected. Coronavirus can cause relatively severe disease, similar to influenza, among frail older patients. Viral coinfections with coronavirus and especially RSV are reported frequently (Pyrc et al., 2007, Gaunt et al., 2010). Vaccines against SARS-CoV-2 and its variants effectively protect from severe disease (Graña et al., 2022).

Human metapneumovirus is a relatively new discovery: a single-stranded, negative-sense RNA virus, first documented in the Netherlands in 2001 (van den Hoogen et al., 2001, van den Hoogen et al., 2002, Hamelin & Boivin, 2005). It belongs to the *Pneumoviridae* family and can cause a wide range of respiratory diseases from mild upper respiratory tract infection to severe bronchiolitis and pneumonia (van den Hoogen et al., 2001, Agapov et al., 2006). It is closely related to RSV but seldom causes symptomatic disease in healthy older people (Jartti et al., 2011). However, it has been reported that during metapneumovirus outbreaks up to 72% of the institutionalized older people may get ill, 50% even lethally (Boivin et al., 2007, Louie et al., 2007). In a prospective study, consisting of 508 study patients over 50, hospitalized because of acute respiratory illness, Widmer et al. analyzed from nasal/throat swabs the presence of RSV, influenza virus and human metapneumovirus. The rates of presence of the viruses were 6.1%, 6.5% and 4.5% respectively, and annual hospitalization rates were considered similar when compared with each other. When compared to patients with influenza virus, patients with human metapneumovirus were older, had more cardiovascular diseases, had more often had influenza vaccination and had less often reported fever. (Widmer et al., 2012) Overall, the clinical symptoms caused by human metapneumovirus are indistinguishable from respiratory syncytial and influenza virus infections (van den Hoogen et al., 2004). Falsey et al. reported in their cohort study that human metapneumovirus circulates in all age groups but is most common among young adults. Geriatric patients seemed to suffer more often from dyspnea and wheezing when compared with young ones, and frail seniors needed

medical attention more often than healthy seniors. (Falsey et al., 2003) Human metapneumovirus has also been documented as causing serious outbreaks in long-term care facilities. Preventive actions and outbreak management should be planned, becaise there is no vaccine available against human metapneumovirus (Centers for Disease Control and Prevention (CDC), 2013, Spires et al., 2017).

Human adenovirus was originally isolated from patients with febrile respiratory infection but has been associated with numerous clinical manifestations. Adenoviruses consist of linear double-stranded DNA genomes and belong to the *Adenoviridae* family. They can infect many different cell types (originally found from adenoid tissue) and are thus studied as potential vectors for gene delivery to develop innovative new treatments for diseases like cancer and cardiovascular disorders. There are more than 51 serotypes that can infect humans, divided into 7 species, A-G. Types B, C and E cause acute respiratory disease in humans. Adenovirus usually causes a mild self-limiting disease but may also cause local outbreaks with severe course especially among immunocompromised patients, children and older patients. (Lion, 2014, Jones et al., 2007, Scott et al., 2016) According to compiled data from around the world, it seems that adenoviruses can cause respiratory diseases endemically and in epidemics. Furthermore, epidemiological data suggest that 5%–15% of acute upper and around 5% of lower respiratory tract infections in childhood are caused by adenovirus. (Kajon et al., 2019) There is little information about the significance of adenovirus among the older population, but at least one severe outbreak in a long-term care facility has been described (Kodama et al., 2017, Kandel et al., 2010).

Human enteroviruses belong to the same *Enterovirus* genus in the *Picornaviridae* family together with human rhinoviruses and are non-enveloped, positive-stranded RNA viruses. The genus is divided into seven human species, of which four are enteroviruses. Unlike rhinoviruses, enteroviruses can resist body temperature and acidic conditions in the gastrointestinal tract and are thought to be able to infect through swallowing. Enteroviruses can infect a wide spectrum of different cells and thus can cause diverse clinical syndromes. Enterovirus types C and D cause respiratory infections like human rhinoviruses. (Royston & Tapparel, 2016, Tapparel et al., 2013, Hyypiä et al., 1997) Enterovirus commonly causes pediatric symptoms varying from mild respiratory symptoms to severe conditions like encephalitis, myocarditis, and neonatal sepsis. However, lower respiratory infections have also been reported and severe respiratory diseases may also occur among older patients with underlying comorbidities. (Jacobson et al., 2012, Lau et al., 2016) There is no vaccine to protect against human enteroviruses.

Human bocavirus (BoV) was found from respiratory secretions of children with respiratory infection in 2005 (Broccolo et al., 2015, Allander et al., 2005). Human bocavirus belongs to a large *Parvoviridae* family, which is divided further into subfamilies having only two other human infecting viruses. Parvoviruses have a linear single-stranded DNA genomes and they replicate only in dividing cells. (Lindner & Modrow, 2008) Three other human bocaviruses have been found later from stool samples and named human bocavirus 2, 3 and 4. Human bocavirus 1 seems to be the only one associated with respiratory illness. It has been reported to cause severe respiratory illness also in adults although it is most common in infants under 2 years of age (Bastien et al., 2006). Human bocavirus infection cannot be clinically differentiated from other viral respiratory infections and illnesses affecting both upper and lower respiratory tract have been described. However, the pathogenic value of human bocavirus is still discussed as very often other viruses are also present in patients with respiratory symptoms and bocaviruses have been found also from asymptomatic control patients. (Peltola et al., 2013, Allander et al., 2007, Söderlund-Venermo et al., 2009) Lindner et al. found IgG antibodies against human bocavirus from 94% of 299 healthy adult blood donors, which suggests high prevalence of this virus in general population. Söderlund-Venermo et al. reported similar results with 96% immunity among 115 healthy adults. (Söderlund-Venermo et al., 2009, Lindner et al., 2008) Bastien et al. analyzed 1209 respiratory tract samples for bocavirus from all age groups suffering from undiagnosed acuter respiratory illness and could not show difference in infection rates between different age groups (Bastien et al., 2006). There is lack of knowledge about bocavirus infections among adults and older adults as studies have focused mainly on children by far (Jartti et al., 2011, Allander et al., 2005, Peltola et al., 2013, Allander et al., 2007, Söderlund-Venermo et al., 2009, Bastien et al., 2007). There is no vaccine against human bocavirus available.

2.3.2 Bacterial pathogens

Streptococcus pneumoniae is the most common pneumonia-causing bacterium (Henriques-Normark & Tuomanen 2013, Torres et al., 2014). This gram-positive bacterium was found in 1881 and was called pneumococcus for a long time because of its ability to cause pulmonary disease. In the same decade pneumococcus was linked to meningitis and otitis media; today, *Streptococcus pneumoniae* is known to colonize the upper respiratory tract frequently and to cause, for example, otitis media, sinusitis, bronchiolitis, pneumonia, arthritis, nosocomial infections, endocarditis, peritonitis, and sepsis (Watson et al., 1993,

Engholm et al., 2017, Bouza et al., 2005, Sopena et al., 2005, Bogaert et al., 2004). Illnesses caused by *Streptococcus pneumoniae* most commonly affect the youngest and the oldest individuals in our population. The peak nasopharynx colonization rate of over 50% of *Streptococcus pneumoniae* seems to occur in 3-year-old children and declines after that steadily under 10% until the age of 10. (Bogaert et al., 2004, Regev-Yochay et al., 2004) Regev-Yochay et al. reported in their study that differences between adults and older adults in *Streptococcus pneumoniae* colonization rate could not be shown, with both around 4% (Regev-Yochay et al., 2004). Antibiotic treatment of pneumococci infections has been recently complicated because of antibiotic-resistant strains. There are also seven valent vaccinations available, which are effective against vaccine-type strains but gives no protection against other strains. Regev-Yochay et al. reported vaccine covers of 42% of the strains carried by children and 21% of the strains carried by adults. (Bogaert et al., 2004, Regev-Yochay et al., 2004) Clinical symptoms of *Streptococcus pneumoniae* infections are variable, and blood culture is the most important tool for establishing a definitive diagnosis (Ortqvist et al., 2005, Torres et al., 1998).

In addition to *Streptococcus pneumoniae*, there are several less commonly pneumonia-causing pathogens, the most common being *Mycoplasma pneumoniae, Haemophilus influenzae* and *Chlamydia pneumoniae* (Torres et al., 2014).

2.4 Diagnostics of respiratory diseases

Diagnostics of respiratory diseases have evolved rapidly last decades by means of PCR diagnostics, good availability of inflammatory laboratory tests, and more accurate imaging. However, challenges also remain as interpretation of clinical symptoms and specimen collection for pathogen analysis remain difficult.

2.4.1 Incubation, signs, and symptoms

The lengths of incubation periods vary considerably between different viruses causing respiratory infections. Symptoms may start as soon as 10–12 hours after infection, as with some rhinovirus types, or even take seven days to appear, as with some influenza types. (Heikkinen & Järvinen, 2003, Harris & Gwaltney, 1996) The mean duration of common cold symptoms is typically 7 to 10 days (Puhakka et al., 1998).

The most common pneumonia causative, *Streptococcus pneumoniae*, is not considered contagious, but outbreaks can occur in crowded living conditions. Median durations for *Streptococcus pneumoniae* carriage is 2 to 4 weeks (Ekdahl et al., 1997, Musher, 2003). With the two second-most common bacteria, the incubation period with *Mycoplasma pneumoniae* varies from 2 to 3 weeks and with *Chlamydia pneumoniae* is even several weeks (Foy et al., 1966, Kuo et al., 1995, Woodhead, 2002).

Typical symptoms in respiratory infections are sore throat, nasal stuffiness and discharge, sneezing, cough and often hoarseness, headache, malaise, and lethargy. Fever is not a typical rhinovirus infection symptom in adults but is common in children with an upper respiratory infection. Myalgia is also present sometimes, although more typical in influenza infection. (Heikkinen & Jarvinen, 2003)

As respiratory viruses may be both causative as well as predisposing agents to pneumonia, the symptoms at the onset of pneumonia also overlap a great deal (Ruuskanen, 2011). The most common symptoms present in pneumonia are cough and fever (Flanders et al., 2004). Fever should lead to suspicion of pneumonia rather than the common cold (Heikkinen & Järvinen, 2003). Other symptoms typical of pneumonia are malaise, chills, headache, myalgia, dyspnea and pleurodynia, and the most common clinical observations are rales, tachypnea, tachycardia, expectoration, and dull percussion sounds. Not one of these is specific to pneumonia. (Flanders et al., 2004, Bochud et al., 2001, Metlay & Fine, 2003) With older patients, pneumonia symptoms are often subtler, and atypical symptoms like syncope or falls may occur (Flanders et al., 2004, Chen et al., 2010, Metlay et al., 1997).

2.4.2 Microbiological testing

A causative viral agent can be shown from up to 90% of patients with respiratory infections by means of viral culture, antigen tests and PCR tests (Ruuskanen & Heikkinen, 2011). In pneumonia patients, determining the causative pathogen is hard; sample collection from the infection focus is challenging, and mixed infection with viruses predisposing to bacterial disease is common (Korppi & Järvinen, 2011). Viral infections cause 13% of community-acquired pneumonias in adults (National Institute for Health and Care Excellence, 2022). Hohenthal et al. stated that pneumonia episodes with a respiratory virus also detected were relatively common among adults, and these episodes were also often severe (Hohenthal, 2009). Microbiological testing may give valuable information when the probability of changing the empirically started antibiotic is high. Positive blood or pleural fluid culture gives the definitive answer of causative bacterial

pathogen, but samples from the respiratory tract need more interpretation because colonization without infection is also possible. (Prina et al., 2015) Still, it is unclear whether routinely taken PCR nasopharyngeal swab samples from older patients with respiratory symptoms could give clinically relevant information.

2.4.3 Inflammatory parameters

Blood tests from patients with suspected pneumonia can provide valuable information about inflammatory state, disease severity and associated organ morbidity (Prina et al., 2015). In aiming to reduce the use of antimicrobial drugs in patients with suspected lower respiratory tract disease in primary care, the use of C-reactive protein (CRP) in differentiating viral diseases from bacterial disease seems to be effective (Aabenhus et al., 2014). Moreover, especially high CRP values seem to associate with more severe disease (Almirall et al., 2004). Hohenthal et al. showed that CRP over 100 after four days of hospital care is associated with poor treatment response and complications (Hohenthal, 2009). The use of procalcitonin to differentiate bacterial disease from other respiratory diseases has increased recently, and meta-analyses have shown that its use may result in lower risks of mortality, lower antibiotic consumption and lower antibiotic-related side effects (Schuetz et al., 2017).

LL-37 is an important human antimicrobial peptide (Lai & Gallo, 2009). It invites neutrophils, monocytes, and dendritic and T cells to act and is released by epithelial cells and leukocytes after infection (Bandurska et al., 2015). It can be found in the human lung where it may have antimicrobial activity at the airway surface (Bals et al., 1998). For example, LL-37 has shown antiviral activity against RSV in vitro (Currie et al., 2013). Serum LL-37 concentration in bacterial pneumonia patients has been elevated compared with healthy subjects (Majewski et al., 2018). Interestingly, LL-37 in lung epithelium may be upregulated by serum 25(OH)D (Hansdottir et al., 2008). In a study of older sepsis patients, LL-37 was indicated to have predictive value in 28-day survival (Castañeda-Delgado et al., 2013, Guo et al., 2018). However, altogether, clinical studies concerning serum LL-37 among older patients are scarce, and its potential usefulness in clinical work is unknown.

2.4.4 Imaging

Chest radiograph remains the first-line radiographic tool in diagnosing community-acquired pneumonia because it is cheap and its availability is good

(Vilar et al., 2004). However, it has also its limitations. Chest radiographs give only very limited information about causative agents (Boersma et al., 2006). Interstitial infiltrates are believed to suggest viral etiology of pneumonia, but bacteria and viruses alone and together may cause a variety of radiographic changes, and microbial cause can´t be defined based on chest radiograph only (Ruuskanen, 2011). Sometimes computer tomography is needed when clinical suspicion of pneumonia is high and a chest radiograph can´t reveal the pathology (Kitazawa et al., 2020).

2.5 Risk factors

There are two types of risk factors for pneumonia: erasable and non-erasable. Age and often also comorbidities are nonerasable. Meticulous treatment of comorbidities is often possible, though. Advancing age and immunosenescence related to it are factors that cannot be altered. In contrast, nutrition, medications, and many lifestyle factors are indeed potential erasable risk factors for pneumonia.

2.5.1 Age and immunosenescence

Aging is a well-known risk factor for respiratory infections as well as parenchymal lung diseases and primary lung cancer. Many different age-related pulmonary dysfunctions have been proposed to explain the increased susceptibility to respiratory tract infections. (Schneider et al., 2021) The increased susceptibility to infections may be due to impaired immune function, frailty and increasing exposure (Haq & McElhaney, 2014). Lower respiratory tract infection incidence increases significantly with advancing age (Meyer, 2010, Meyer, 2004). Weakened cough reflex, mucosal barrier function, and mucociliary clearance are features of the aged respiratory system that predispose humans to pneumococcal infection. Cell-mediated and acquired humoral aspects are shown to decline with increasing age. Many recovery and defense-impairing structural and functional changes have been described in respiratory systems with advancing age. (Meyer, 2005, Schneider et al., 2021) Aging thoracic spine and ribs lead to decreased thoracic and breathing volumes, and wakened intercostal muscles make airway cleaning functions less efficient (Haq & McElhaney, 2014). Overall, age-related risk factors behind increased susceptibility of older adults to pneumonia are numerous: dysfunctional immune defense, predisposition to aspiration, depressed clearance mechanisms, medical care facilities admissions, organ system

dysfunctions, malnutrition, smoking, alcoholism, and viral infections. (Meyer, 2005)

The deterioration of innate and adaptive immunity along with biological aging is called immunosenescence (Haq & McElhaney, 2014). Immunosenescence shows itself in poorer vaccination responses, worse anti-cancer responses, increased inflammation and tissue damage, autoimmune reactions, and increased susceptibility to common respiratory viruses like influenza (Haq & McElhaney, 2014, Pawelec, 2018). Immunosenescence is associated with deteriorated activation of both innate and adaptive immune responses. The impaired innate response is primarily caused by worse functioning of neutrophils, monocytes and dendritic cells, whereas the worsening of adaptive immunity is caused by reduced ratio of naïve memory T cells. (Haq & McElhaney, 2014)

2.5.2 Comorbidities, oral health, and dysphagia

The likelihood of developing a chronic lung diseases like COPD, interstitial fibrotic lung disease, or lung cancer increases with advanced age (Schneider et al., 2021). These chronic conditions predispose older people to acute infections. In addition to infection-predisposing diseases, older citizens also have more often resilience- and recovery-impairing chronic diseases. In trying to predict which community-acquired pneumonia progresses into severe, possibly intensive care-requiring pneumonia, different scoring systems for prognosis have been introduced (Marti et al., 2012). From the most used scores, pneumonia severity index and CURB-65, the first mentioned gives relatively large weight to chronic conditions: history of renal disease, cerebrovascular disease, liver disease, neoplasm, congestive heart failure (Cabre, 2009). Interestingly, there is no clear evidence that COPD would increase mortality among pneumonia patients (Ma et al., 2020; Molinos et al., 2009).

Oral health is important and a far too often neglected risk factor for pneumonia, among other pathologies (Chebib et al., 2021). Mortality due to pneumonia among older patients with ten or more of their own teeth was almost 4 times higher in patients having over 4 mm periodontal pockets than in patients with smaller pockets, indicating better oral health (Awano et al., 2008). Sjögren et al. conducted a systematic review to evaluate the preventive effect of oral hygiene on pneumonia and respiratory tract infection among older patients in hospitals and nursing homes. They stated that 1 of 10 pneumonia-caused deaths among older nursing home residents could be prevented by improving mechanical oral hygiene. (Sjögren et al., 2008)

Oropharyngeal dysphagia is known to be a major aspiration pneumonia-predisposing condition among older people. Aspiration of mouth or gastric contents is often the result of impaired swallowing, and weak cough reflex typical in older people makes it even more probable. In addition to dysphagia and weak cough reflex, risk factors for macroaspiration-associated pneumonia are impaired consciousness and increased change of gastric contents reaching the lung. Swallowing can be impaired for multiple reasons, such as esophageal diseases, COPD, neurologic conditions, and mechanical ventilation extubation. Multiple causes such as alcohol use, taking certain medicines, neurologic diseases, and dementia impair consciousness and cough reflex. (Mandell & Niederman, 2019)

2.5.3 Nutrition and medications

Low body weight and recent weight loss among over-65-year-old immunocompetent people seem to associate with greater risk of developing community-acquired pneumonia (Jackson et al., 2009). Moreover, malnutrition seems to be associated with poor long-term outcome among older people with community-acquired pneumonia (Yeo et al., 2019). Until the last 20 years, hypoalbuminemia was considered a specific nutritional marker with lower serum values among malnourished people. More recently it has been acknowledged that serum albumin level is influenced by many factors. Inflammation especially – both acute and chronic – decreases serum albumin level. However, in addition to the inflammation, nutritional risk also seems to associate with low serum albumin levels. (Eckart et al., 2020) Moreover, all-cause mortality among coronary syndrome patients seems to be associated with low serum albumin level (Zhu et al., 2020).

Hypoalbuminemia is associated with mortality, morbidity, and worse recovery after acute pathologies among older patients (Cabrerizo et al., 2015, El-Solh et al., 2003). Decreased albumin level is associated with inflammatory state and reduced longevity (Soeters et al., 2019). Serum albumin level below 3.5 g/dL is defined as hypoalbuminemia among adults, and thus also among older adults, but often only levels below 2.5 g/dL arouse clinical interest (Gatta et al., 2012). Malnutrition is still often discovered through decreased albumin levels alone, although more accurate methods are recommended. The condition is associated with poor clinical outcome in many diseases. (Demir & Özbek, 2021, Shirakabe et al., 2018). Lowered serum albumin levels have also been linked to short-term mortality risk during hospital care (Akirov et al., 2017, Hedlund, 1995, Liu et al., 2015). For these reasons, extra caution in treating community-acquired

pneumonia patients with low serum albumin levels has been suggested (Hedlund, 1995).

Multiple health benefits have been suggested for vitamin D as its receptors exist in most tissues and cells in the body (Holick et al., 2011). Deficiency is defined as serum 25(OH)D below 20 ng/ml (50 nmol/liter), and 25(OH)D insufficiency as a 25(OH)D of 21–29 ng/ml (52.5–72.5 nmol/liter) by the Endocrine Society (Holick et al., 2011). Association between serum 25(OH)D deficiency and frailty is well established (Wong & Flicker, 2015, Walston et al., 2006). Even survival of ambulatory older ccitizens and associations between serum 25(OH)D concentration and respiratory disease morbidity have been shown (Bjelakovic et al., 2014, Kim et al., 2015, Holter et al., 2016, Quraishi et al., 2013, Monlezun et al., 2015). Fisher et al. found in their study consisting of 1820 low-energy hip fracture patients that 25(OH)D level less than 25 nmol/L was associated with in-hospital mortality. However, association as continuous variable could not be shown. (Fisher et al., 2018)

Certain medicines have been linked to increased susceptibility to pneumonia. Drugs that suppress immunological responses, oral and inhaled corticosteroids, proton pump inhibitors and antipsychotics have been reported to increase the risk of pneumonia (Almirall et al., 2017; Chebib et al., 2021).

2.5.4 Environmental and lifestyle factors

Environmental factors, in addition to the individual's personal factors, may affect the risk of pneumonia. Poor ventilation in crowded housing, low socioeconomic status, contacts with children, and air pollution are factors that increase the risk of pneumonia. There is some evidence that alcohol use could protect against pneumonia but only if the consumption is reasonable – no more than three alcohol doses a day (40g or less). Greater alcohol usage increases the risk of pneumonia. Smoking, current or former, increases the risk of pneumonia. (Torres et al., 2013)

2.6 Prevention

Prevention of pneumonia consists of erasing the removable risk factors and vaccinating against pathogens that cause bacterial pneumonia, but possibly also against influenza virus.

In short there are five pathogens against which vaccines are available for older adults: *Streptococcus pneumoniae*, influenza virus, herpes zoster virus, SARS-CoV-2, and RSV (Antonelli Incalzi et al., 2020, U.S. Food & Drug administration,

2023, Graña et al., 2022). Some association between influenza vaccination and reduced pneumonia incidence and better outcomes has been shown (Heo et al., 2018; Prina et al., 2015). The association could be explained by reducing the incidence of influenza and thus also post-influenza pneumonia (Heo et al., 2018). There are two commercial vaccines against *Streptococcus pneumoniae*, PPV23 and PCV13. Immunizing the older population with both vaccines to overcome single-vaccine disadvantages is justified (Kim et al., 2017). The vaccine against RSV was approved by the U.S. Food & Drug administration in May 2023 for individuals 60 years of age and older (U.S. Food & Drug administration 2023).

To prevent pneumonia, in addition to vaccination, reducing risk factors is crucial. Suggested risk factors that can be eliminated are, for example, smoking, environmental exposures, poor nutritional status, functional impairment, poor oral health, immunosuppressive therapy, oral steroids, and treatment with proton pump inhibitors or H2 antagonists (Almirall et al., 2017).

3 Aims

The aims of this thesis were to investigate the presence of respiratory viruses among older citizens with hospitalization-requiring illness and to evaluate whether there are associations between viruses found and disease severity and/or chronic illnesses. We studied whether the presence of a respiratory virus could give clinically relevant information when treating older patients with respiratory symptoms and suspected pneumonia. Moreover, we studied whether serum 25(OH)D, albumin, and LL-37 levels in older patients with acute respiratory disease could provide long-term prognostic value.

The specific aims of each study are presented below:

I To investigate the presence of viruses in the aged and to assess the association of virus detection with the presence and severity of respiratory illness and with chronic illnesses in individuals with a hospitalization-requiring illness.

II To study how viral pathogens detected in the nasopharynx and conventional inflammatory markers (white blood cell count and CRP) correlate to signs, symptoms, or prognosis of pneumonia among aged.

III To investigate the prognostic value of serum 25(OH)D, albumin, and LL-37 levels in acute respiratory diseases among aged.

4 Materials and Methods

4.1 Subjects

Patient recruitment for the studies took place in Turku City Hospital between July 2007 and April 2009 as a cohort. Consecutive over-65-year-old patients residing in Turku and suffering from respiratory symptoms that required hospital admission were recruited. In addition, control group patients without respiratory symptoms for study I were recruited from September 2007 to May 2008. Patients with coryza, cough, sore throat, hoarseness, or nasal stuffiness were considered to have respiratory symptoms. The need for oxygen was considered a sign of dyspnea. Written consent from the patient or their trustee was required to participate in the study.

Patients who were admitted for a short elective operation or who had taken part in the study less than 2 weeks before were excluded from the study. Patients were excluded if they needed transfer to other institutions, were in extremely poor condition, had severe dementia, or had been quarantined. “Extremely poor condition” was defined as having less than a few months left to live as evaluated by a study physician.

In study I, 438 hospital episodes with respiratory symptoms and 291 hospital episodes without symptoms were recorded. The mean age in both groups was 83 ± 7. Asthma, chronic obstructive pulmonary disease (COPD), and rheumatic diseases were more common, and hypertension, stroke, dementia, and depression less common, in episodes with respiratory symptoms than in those without.

In study II, 382 consecutive episodes with respiratory symptoms and available chest radiograph were screened. The mean age among these patients was 83 ± 7 years, and 112 had pneumonia findings in chest radiographs.

In study III, 298 episodes with sufficient serum sample for vitamin D, LL-37 and albumin analysis were further followed for 5 years. The mean age of these patients at the beginning of follow-up was 83 ± 7.

4.2 Clinical follow-up

In all studies I–III, patients or their trustees were interviewed using a standardized questionnaire considering their form of living, chronic diseases, influenza vaccination status, height, weight, smoking habits, and physical activity. In addition, hospital records were reviewed for clinical history. Having cardiovascular, respiratory, and other diseases was recorded. Having dementia, depression, diabetes, rheumatic disease, or history of cancer was defined as having other diseases. Cognition was assessed with Mini-Mental State Examination (MMSE) score (Folstein, Folstein et al., 1975).

The presence of all common respiratory viruses was screened in all studies from nasopharyngeal swabs using PCR. The length of hospital stay, later hospital revisit, and death during the hospital stay were used as clinical outcomes of study II. The study radiologist analyzed chest radiographs taken during treatment in a blinded fashion for studies II and III. After congestive heart failure as an etiology was excluded, interstitial infiltrate and/or lobar atelectasis were considered pneumonia. Dates of death during follow-up time were searched from hospital records in study III.

In all studies, patients were discharged when illness no longer required hospital treatment, and later hospital revisits were recorded only when respiratory symptoms were present. A new hospital episode less than 2 weeks from the last visit was considered prolonged illness and, after 6 months, a separate episode.

In study III, hospital records were reviewed for the use of vitamin D supplements and physical activity of daily living (ADL) scores. ADL-scores were defined as: 1 = bedfast, 2 = requires assistance, 3 = self-sufficient, poor mobility, 4 = self-sufficient, exercises outdoors regularly. Deaths after 1, 2 and 5 years were predefined primary outcomes of study III. Virus presence in the nasopharynx, severity of disease, hospital stay length, hospital revisit, and mortality during hospital stay were used as secondary outcomes. In both studies II and III, the severity of respiratory tract disease was estimated based on the presence of pneumonia, dyspnea and CRP and white blood cell (WBC) levels. In study III, 25(OH)D deficiency was defined as serum 25(OH)D level below 50 nmol/liter (20 ng/ml) and hypoalbuminemia as serum albumin level below 3.5 g/dL (Holick et al., 2011, Gatta et al., 2012).

4.3 Sample collection and analysis

In all studies I–III, nasopharyngeal swab samples (sterile flocked swab, 520CS01, Copan, Brescia, Italy) were collected on hospital admission. They were stored in dry tubes in a refrigerator for a maximum of 24 hours before transportation to the

laboratory, where they were stored at -70 °C until virus PCR analyses. In addition, blood was drawn from patients with respiratory symptoms on admission and the serum samples were stored at -80 °C.

Swab samples were analyzed by a multiplex reverse transcriptase-PCR (RT-PCR) test (Seeplex RV12 ACE Detection; Seegene, Seoul, Korea) for adenovirus, coronavirus NL63 and OC43, human bocavirus, MPV, influenza A and B, PIV1–3. Testers used an "in-house" RT-PCR for RSV, RV (including rhinovirus type C), and enteroviruses at the Department of Virology, University of Turku, Turku, Finland (Turunen et al., 2014). Based on our previous experiences from sequencing of the amplicons, if the in-house PCR could not distinguish enteroviruses from rhinoviruses, the result was considered rhinovirus positive (Nicholson et al., 1997, Jartti et al., 2009). Human bocavirus infections were serologically confirmed at the Department of Virology, University of Helsinki, Helsinki, Finland.

Serum samples underwent BoV1-specific virus-like particle (VLP)-based IgM and IgG competed enzyme immunoassay, and those of suspected acute cases also underwent BoV1 and 2 quantitative (q)PCR, at the Department of Virology, University of Helsinki, Finland, as previously described (Kantola et al., 2011, Kantola et al., 2010). Furthermore, the swab samples underwent BoV1-4 multiplex qPCR, analyzed in pools of two, and all PCR-positive pools were opened and analyzed individually by both multiplex and singleplex BoV1-4 qPCRs (Kantola et al., 2011). The definition of an acute BoV1 infection was IgM positivity accompanied with a seroconversion or diagnostic rise in IgG or viremia, whereas a BoV1 PCR-positive swab sample alone cannot state the acuteness of the infection (Soderlund-Venermo et al., 2009).

In all studies, blood samples for CRP and WBC analysis were routinely collected as part of hospital treatment and analyzed by the hospital laboratory from all the patients. The highest values of CRP and WBC were used in statistical analysis.

In study III, from the same serum samples taken primarily for bocavirus analysis, serum levels of 25(OH)D, albumin, and LL-37 were analyzed at Massachusetts General Hospital. Serum 25(OH)D level was analyzed using immunoassay (Abbott Architect, Chicago, USA) and LL-37 was measured using ELISA (Hycult Biotech, Uden, the Netherlands), both in Massachusetts General Hospital, Boston, USA (Elenius et al., 2017).

4.4 Statistical methods

In study I, t-test, Wilcoxon's rank sum test, $\chi 2$ test and Fischer exact test (when counts < 5) were used in basic statistics. Univariable logistic regression was used to

analyze the association between virus etiology and chronic illnesses, age, weight, and symptom severity.

In study II, two sample t-test, $\chi 2$ test and Fischer exact test were used when appropriate, respectively. Logistic regression with backward stepwise elimination was used to analyze the association between clinical outcomes and virus etiology, pneumonia, chronic illnesses, age and laboratory findings: the model iteratively removed the least useful predictor for clinical outcomes, one at a time, until only significant predictors were left.

In study III, patient characteristics of patients with pneumonia versus patients without pneumonia were compared using two-sample t-test, $\chi 2$-test, and Fisher exact test, as appropriate. Multivariable Cox regression analysis was used to test the associations between clinical variables and 1-, 2- and 5-year survival. Multivariable logistic regression was performed to examine the association between serum 25(OH)D, albumin, and LL-37 with clinical outcomes after adjusting for age, sex, major chronic diseases, presence of a respiratory virus and usage of vitamin D supplement. The associations of clinical variables mentioned above with serum CRP and WBC were analyzed using linear models. Natural logarithm-transformed values for serum 25(OH)D, LL-37, CRP and WBC were used in the models due to positively skewed distributions.

In all studies, results are expressed using adjusted odds ratios (OR), mean differences, regression coefficients and hazard ratios (HR) with their 95% confidence intervals (CI). P-values $< .05$ were considered statistically significant. Statistical analyses were performed with SAS System for Windows, version 9.4 (SAS Institute Inc., Cary, NC, USA).

5 Results

5.1 Study population

For studies I, II and III, a total of 921 episodes of hospital care were screened as a cohort. Only 43 patients refused to participate in the study and 149 were not eligible.

In the end, 438 hospital episodes fulfilled the initial study requirements of age 65 or over, hospitalization-requiring disease, respiratory symptoms, and a signed consent to participate in the study.

In study I, nasopharyngeal swab samples were collected from all 438 episodes, and from 389, serum samples for bocavirus serology also. In addition, to serve as a reference group, 291 nasopharyngeal swab samples and 289 serum samples from patients without respiratory symptoms were collected.

In study II, chest radiographs were available from 348 of the above mentioned 438 episodes; in 56 of the visits, a chest radiograph was not available, and 34 episodes were excluded from study II as secondary visits.

In study III, from the study II cohort, sufficient serum samples for D-vitamin, albumin and LL-37 analysis were available from 289 patients. These 289 patients were followed for 5 years.

5.2 Patient characteristics

In study I, the mean age in both groups, with and without respiratory symptoms, was 83 years (standard deviation (SD) 7, Table 2). Asthma/chronic obstructive pulmonary disease and rheumatic diseases were more common in the episodes with respiratory symptoms whereas hypertension, stroke, dementia, and depression were less common when compared to the episodes without respiratory symptoms (all $P < .05$). Respiratory patients with dyspnea differed from those without dyspnea by having more COPD/asthma and other lung diseases, heart failure and diabetes (all $P < .05$)

Table 2. Patient characteristics in study I.

Characteristics	Respiratory symptoms			
	Any	With dyspnea	Without dyspnea	No
	n=438 (%)	n=200 (%)	n=238 (%)	n=291 (%)
Gender (men/women)	***45/55*** [a]	48/52	42/58	30/70
Age, years	82.9 (7.2)	83.0 (6.9)	82.9 (7.5)	82.9 (7.1)
Weight, kg	67.8 (16.9)	***70.0 (17.9)*** [b]	65.8 (15.7)	66.3 (16.6)
Respiratory diseases	***34*** [a]	***46*** [b]	24	18
- Asthma/COPD	***28*** [a]	***40*** [b]	17	13
- Other lung disease	***11*** [a]	***14*** [b]	7.8	5.2
Cardiovascular disease	***75*** [a]	72	77	89
- Stroke/TIA	***15*** [a]	15	15	31
- Heart dysrhythmia	28	30	26	30
- Myocardial infarction	***15*** [a]	14	16	21
- Heart failure	***25*** [a]	***30*** [b]	20	33
- Hypertension	***48*** [a]	44	51	60
- MCC	33	30	35	36
Other diseases	***65*** [a]	67	64	79
- Dementia	***23*** [a]	21	24	37
- Depression	***7.0*** [a]	7.3	6.8	13
- Rheumatic disease	***28*** [a]	24	30	12
- Diabetes mellitus	[a]	[b]		
-Type 1	***0.48***	***0.0***	1.0	0.34
- Type 2	***21***	***28***	16	31
- Cancer status	[a]			
- Terminal	***2.7***	2.6	2.7	4.1
- Have been treated	***10***	13	8.6	23
- Under treatment	***6.3***	7.8	5.0	4.5
Smoking	31	36	25	32

Data expressed as % or mean (standard deviation).
Chi-squared test and Fischer exact test (when counts<5) were used.
Significant values are shown bold and italic.
[a] Differs (P < .05) from episodes without respiratory symptoms.
[b] Differs (P < .05) from episodes with respiratory symptoms without dyspnea.
COPD, chronic obstructive pulmonary disease
TIA, transient ischemic attack
MCC, morbus coronarius cordis
Modified from Original Publication II

In study II, the mean age of both study groups, with and without pneumonia, was 83 (SD 7) years. Overall, cardiovascular disease was present in 74% and respiratory disease in 34%, and no statistical difference was seen between study groups. In pneumonia episodes, weight was lower than in episodes without pneumonia (P = 0.05). Heart dysrhythmia and history of stroke or transient ischemic attack (TIA) seemed to be more common among patients without pneumonia (P = .03 and P = 0.08, respectively). Smokers tended to have pneumonia more often than nonsmokers, but statistical difference could not be established (P = .098). Otherwise, differences in the prevalence of cardiovascular, respiratory, and other diseases were not seen in episodes with pneumonia and episodes with respiratory symptoms without pneumonia (all P > .1).

In study III 57% of the patients were female. The mean age of male patients was 81 (SD 7); female patients, 84 (SD 7); and together, 83 (SD 7) years (P = .001). Pneumonia was more common among male patients (54%, P = .02). A diagnosis of cardiovascular and respiratory disease was present in 77% and 31%, respectively. Up to 71% had other disease (dementia, depression, diabetes, rheumatic disease, or history of cancer). Vitamin D supplement was taken by 36% of the study patients. ADL scores were distributed as follows: ADL 4 with 89 (32%), ADL 3 with 107 (38%), ADL 2 with 72 (26%) and ADL 1 with 14 (5%) patients, with ADL 1 being the least and ADL 4 the most self-sufficient.

5.3 Virus detection

Virus epidemics among older adults followed the documented epidemics in the region (Figure 1). In patients with respiratory symptoms, the most common virus was influenza with 42 (10%) positives, followed by RV with 37 (8%), PIV with 33 (8%), CoV with 29 (7%), RSV with 26 (6%), MPV with 8 (2%), enterovirus with 8 (2%), BoV1 2/389 (0.5%), BoV2-4 0/389 (0%), and adenovirus with 2 (0%). Two or more viruses were present in 22 (5%) samples and the most common viruses in coinfections were RV (59%) and influenza A virus (32%). The most common virus combination was RV with coronavirus covering 25% of the coinfections. No acute BoV1 infections occurred among the 396 episodes with respiratory symptoms studied by serology. The total IgG seroprevalence was 88%. Five (1%) patients had IgM absorbance values just above cutoff, but due to nonexistent or low IgG in paired sera as well as serum-PCR negativity, they were considered non-specific reactions. Furthermore, no BoV DNA was found in the nasopharyngeal samples of these patients. In addition, in 2/678 (0.3%) patients, low-load BoV1 DNA was detected in the nasopharynx, however, one with co-detection of another virus. Paired serum

samples were available from one of these patients, but they exhibited relatively low and stable BoV IgG absorbance values without IgM or DNA, indicating past infection.

Viruses were found constantly year-round throughout the study. However, rhinovirus epidemics occurred in the falls of 2007 and 2008, a coronavirus epidemic was seen in mid-winter 2007-2008, an RSV epidemic took place in January/February 2008, a metapneumovirus epidemic occurred in December 2008, and an influenza virus epidemic took place in the beginning of 2009 (Figure 1).

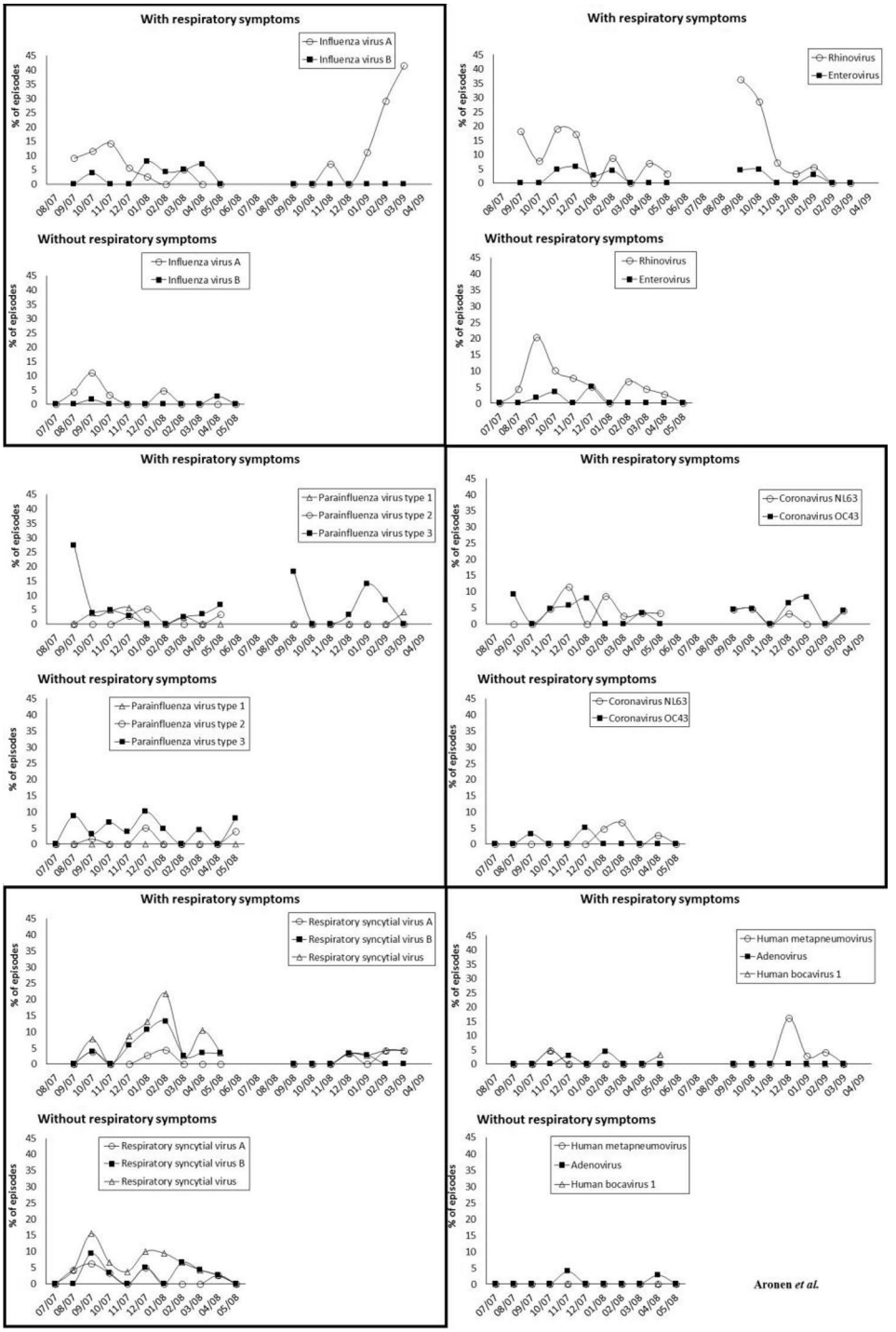

Figure 1. Seasonality of respiratory viruses among patients with and without respiratory symptoms. Data from summer months 2008 not available due to summer holidays.

In patients without respiratory symptoms, there were fewer influenza A, PIV 1, CoV OC43 and metapneumovirus detections than in patients with respiratory symptoms (all $P < 0.05$), and no MPV or BoV1-4 nucleic acids were found. Otherwise, statistical difference between virus presences in swab samples between symptomatic and non-symptomatic groups could not be shown, and even findings with two or more viruses did not statistically differ between these groups ($P = 0.30$). Two or more viruses were detected in 14 (5%) episodes without respiratory symptoms, and the most common viruses there were RSV and RV with 9 (64%) and 8 (57%) coinfections, respectively.

In study II, a respiratory virus was detected from 141/382 (37%) episodes. Overall, rhinovirus and influenza virus were the two most common viruses detected, both present in 35 (9%) cases, followed by PIV, 28 (7%); CoV, 24 (6%); RSV. 22 (6%); MV, 8 (2%); and adenovirus, 2 (1%). Prolonged bocavirus shedding was found in the nasopharynx during one episode (serology did not confirm acute infection). Virus detection tended to be scarcer with pneumonia episodes, but statistical difference could not be shown ($P = .09$). Virus detection overall was not associated with dyspnea in pneumonia episodes ($P > .5$), and no differences in detection of specific viruses between pneumonia groups with and without dyspnea were found either ($P > .1$).

5.4 Virus coinfection

In study I, of the symptomatic episodes, in three out of the four samples with adenovirus, another virus was co-detected. The most common combinations during episodes without respiratory symptoms were RSV with RV and RSV with influenza, accounting for 5 (36%) and 3 (21%) coinfections, respectively. Of the patients with no respiratory symptoms, the most common viruses present with another virus were RSV and RV, present in 9 (64%) and 8 (57%) coinfections, respectively.

5.5 The association between virus etiology and respiratory symptoms

As expected, 160/438 (37%) episodes with respiratory symptoms had more virus detections than 67/291 (23%) episodes without respiratory symptoms ($P < 0.0001$). Specifically, influenza ($P = 0.006$), CoV ($P = 0.005$) and MPV ($P = 0.025$) were detected more often from patients with respiratory symptoms. Among patients with respiratory symptoms, no differences in the presence of respiratory viruses could be shown between episodes with and without dyspnea.

5.6 Associations between virus detections and patient characteristics

In study I, associations between patient characteristics and virus detection were screened. In total 729 hospital episodes were screened, and chronic cardiovascular or respiratory diseases were not associated with respiratory virus detection; neither was smoking (all P > 0.09). Neither was age (range 65, 100 years) associated with detection of respiratory viruses (Table 3). However, patient's weight and the presence of a virus, especially influenza (odds ratio [OR] 1.02, 95% CI .01–1.04) or parainfluenza viruses in the upper airways (OR 1.02, 95% CI 1.00–1.03), were positively associated.

Table 3. Association between respiratory virus presence and age and weight.

	Age	**Weight**
Virus	**OR (95% CI)**	**OR (95% CI)**
Influenza virus	1.01 (0.97–1.05)	***1.021 (1.005–1.038)***
Rhinovirus	1.00 (0.96–1.04)	1.01 (0.99–1.02)
Parainfluenza virus	1.01 (0.97–1.05)	***1.017 (1.000–1.034)***
Coronavirus	0.956 (0.912–1.002)	1.01 (0.98–1.03)
Respiratory syncytial virus	1.02 (0.98–1.06)	0.99 (0.97–1.01)
Human metapneumovirus	0.94 (0.86–1.04)	0.99 (0.94–1.04)
Human bocavirus 1	0.99 (0.82–1.20)	1.03 (0.97–1.09)
Adenovirus	1.00 (0.87–1.14)	1.01 (0.95–1.08)
Enterovirus	1.02 (0.93–1.11)	1.00 (0.96–1.05)
Any virus	1.00 (0.98–1.03)	***1.011 (1.001–1.022)***
More than one virus	1.00 (0.95–1.05)	1.01 (0.99–1.03)

OR (odds ratio)
CI (confidence interval)
Statistically significant results are shown bold and italics.

5.7 White blood cell count and CRP level

In study II, mean WBC values were 11.1 E9/L and 13.8 E9/L among episodes with and without pneumonia, respectively. Association between pneumonia findings in chest radiographs and WBC count as a continuous variable could not be shown (P = 0.07). However, as a categoric variable with WBC count being over or under 15 E9/L, it was associated with pneumonia episodes (P < .006).

The mean CRP values were 146 mg/L and 105 mg/L in episodes with and without pneumonia, respectively (P < 0.001). In episodes with respiratory symptoms, CRP values over 100 mg/L and even over 80 mg/L were associated with a pneumonia finding in the chest radiograph (P < .05).

When comparing pneumonia episodes with and without a respiratory virus, no difference between WBC or CRP values was seen (P > .2). The case was similar with the most common viruses, tested separately: rhinovirus, influenza virus, coronavirus, RSV and parainfluenza virus (P > .1).

5.8 Clinical outcomes

In study II, short-term clinical outcome was available from 357 of the 382 patients with chest radiographs. Overall, 108 had a hospital stay longer than 13 nights, 127 later had a revisit, and 29 passed away during the hospital stay.

The presence of a respiratory virus was not associated with clinical outcomes, number of revisits, over 13-night hospital stays, or deaths at the ward nor with WBC values over 15 E9/L or CRP over 100 mg/L (all P > 0.11). Lower WBC and CRP cutoffs, 10 E9/L and 80 mg/L, respectively, showed similar results. Among pneumonia episodes, association between laboratory findings (WBC over 15 E9/L or CRP over 100 mg/L) and the clinical outcomes mentioned above could not be shown (P > 0.2). Between episodes with and without pneumonia, no difference in number of deaths at the ward was seen. Death at the ward seemed more frequent in pneumonia episodes with dyspnea than in episodes without dyspnea; however, statistical difference could not be shown (P = 0.06). Pneumonia episodes with dyspnea had longer visits than pneumonia episodes without dyspnea (P = .02).

Chronic respiratory diseases, asthma or COPD, tended to be associated with visits shorter than 13 nights among episodes with respiratory symptoms (P = .05). A revisit to the hospital was less probable when a respiratory virus was detected than not; 43 (31%) and 93 (39%) revisits occurred among virus positives and negatives in the same order (P = .05). Death at the ward and CRP value over 100 mg/L were associated with each other; 21 of the 29 (72%) deceased patients had CRP value over 100 mg/L (P = .04).

5.9 Association between serum 25(OH)D level and clinical outcomes

In study III, a majority, 59%, of the 289 study patients had deficient 25(OH)D level below 50 nmol/L. The mean level among study patients was 47 nmol/L (SD 22 nmol/L). There was no association between serum 25(OH)D level nor the use of vitamin D supplement and 1-, 2- or 5-year survival in multivariable Cox regression survival analysis. In logistic regression analysis, serum 25(OH)D level was not associated with clinical outcomes: presence of pneumonia, dyspnea, death at ward, over-13-night visit at ward, revisit, or CRP value over 100 or WBC value over 15. Number of patients with serum 25(OH)D insufficiency seemed similar among patients with (63%) and without (58%) pneumonia (P = .46). No association could be shown between serum 25(OH)D level and maximum CRP and WBC values in linear models.

5.10 Association between LL-37 and clinical outcomes

In study III, mean serum LL-37 level among 289 study patients was 38 ng/ml (SD 32 ng/ml). No associations between serum LL-37 level and 1-year, 2-year or 5-year survival was seen. Serum LL-37 concentration was associated with serum CRP values over 100 mg/L in logistic regression analysis (P = .0006). Similar association was seen between serum LL-37 and CRP and WBC levels in linear models (respectively, P = 0.01 and P = 0.004). However, no association with other clinical outcomes was seen.

5.11 Association between albumin and clinical outcomes

In study III, mean serum albumin level among 289 study patients was 3.4 g/dl (SD 0.4 g/dl). As many as 159 (55%) of the study patients had hypoalbuminemia. High age and low serum albumin level were associated with more probable one-year mortality in multivariable Cox regression analysis (respectively, P < .0007 and P = .0001). In addition to the above mentioned, the presence of other disease (P = .003) was associated with higher 2-year mortality in the multivariable model. Furthermore, the variables mentioned above, and sex and presence of a respiratory virus were

associated with 5-year mortality (respectively, P = .0002 and P = .01). Female sex and virus presence were associated with better 5-year survival.

Among pneumonia patients, hypoalbuminemia was more common (72%) than among patients without pneumonia (49%) (P = .0004). Low serum albumin level was associated with many clinical outcomes: pneumonia, dyspnea, over-13-night stay at ward, death at ward and serum CRP value over 100 mg/L in multivariable logistic regression analysis (P = .01, P = .02, P = .006, P < .0001 and P < .0001, respectively). In predicting pneumonia, in addition to serum albumin level, sex was also statistically significant in the multivariate logistic regression model (P = .049). Female sex seemed to protect against pneumonia. Similarly in predicting dyspnea, in addition to serum albumin level, presence of respiratory disease was statistically significant in the model predicting (OR = 2.79, 95% CI 1.54-5.08, P = .0008). In the model predicting death at ward, age was a statistically significant variable together with albumin (OR = 1.09, 95 CI 1.00-1.17, P = .04).

6 Discussion

6.1 Virus etiology

Study I shows that the most common respiratory viruses in the airways of hospitalized older patients were rhinovirus, influenza virus, parainfluenza virus, RSV, and coronavirus. There was a positive association between patients' weight and virus detection, which could be worth further study. Virus infections overall and namely influenza virus, coronavirus and metapneumovirus infections were more common among hospital care episodes involving respiratory symptoms compared with episodes without respiratory symptoms. The patients with respiratory symptoms more often had respiratory, cardiovascular, and other chronic diseases than patients without respiratory symptoms. These findings remind us of the challenges of virus diagnostics: there are virus detections without infections, and it is not always easy to say whether respiratory symptoms are caused by infection or merely the underlying chronic disease. However, respiratory symptoms do have relevance, and previously diagnosed chronic diseases make them rather more than less important to be noticed.

The proportion of positive virus detection among patients with respiratory symptoms, 37% in our study, is close to previously documented numbers ranging from 11.5% to 42.5% among patents with mean age ≥ 60 (Lieberman, 2010, Pierangeli et al., 2011, Falsey et al., 2002, Atmar et al., 2012, Johnstone et al., 2008, Kaye et al., 2006, Saito et al., 2006, Nicholson et al., 1997, Tanner et al., 2012). The overall number is, however, low when compared with those of children with lower airway illnesses (Rhedin et al., 2012). The bocavirus detection rate in our study was at the same level as previously reported (Longtin et al., 2008). However, previous studies have not confirmed the diagnosis by serology and only a small share of the study subjects were over 65. Rates of metapneumovirus, coronavirus, rhinovirus including group C, and influenza virus in our study were like those reported in previous studies, with over-65-year-old patients (Pierangeli et al., 2011, Falsey et al., 2002, Atmar et al., 2012, Ren et al., 2011, Ren et al., 2009, Johnstone et al., 2008, Falsey et al., 2005, Falsey et al., 2014). Coronavirus, influenza virus, metapneumovirus, RSV and rhinovirus showed clear epidemics. Influenza A, RSV

and parainfluenza virus epidemics among the older citizens followed the documented epidemics in the region, but similar regional adenovirus and influenza B epidemics in early 2009 did not show among our study patients.

The number of viral coinfections was low when compared to studies with patients from all age classes (Tanner et al., 2012, Peci et al., 2013). The most frequent virus in symptomatic coinfections was RV, being present in 38% of the infections. Tanner et al. (2012) reported that rhinovirus was present in 58% of the coinfections in their study with 4821 specimens from all-aged patients with respiratory illness (Tanner et al., 2012). In their study the most common virus combination was rhinovirus, with RSV being present in 2.2% of the samples. There were no symptomatic rhinovirus-RSV coinfections in our study. However, Tanner et al. did not test their samples for coronaviruses, and in our data rhinovirus with coronavirus was the most common combination (Tanner et al., 2012). Overall, it seems that respiratory virus detection from nasopharyngeal aspirate samples may be lower among older than in younger patients, but the rate of coinfections seems to be constant (Tanner et al., 2012, Rhedin et al., 2012, Peci et al., 2013).

Respiratory viruses were detected more often in patients with respiratory symptoms, coryza, cough, sore throat, hoarseness, and nasal stuffiness than in patients with no respiratory symptoms. From simple respiratory symptoms like these, it is impossible to determine which virus, if any, is causing the illness (Navarro-Mari et al., 2005). Among episodes with respiratory symptoms, no differences in the presence of respiratory viruses between episodes with and without dyspnea could be shown in our study or in the one done by Ren et al. (Ren et al., 2009). Our findings are in line with the idea that respiratory virus illnesses commonly trigger serious acute respiratory conditions in patients with asthma and chronic obstructive pulmonary disease (Contoli et al., 2009). In our study, patients with respiratory symptoms had more asthma/COPD than patients without respiratory symptoms. Up to 40% of patients with lower respiratory symptoms had asthma/COPD. However, no links between specific virus infections and chronic diseases were noted. Asymptomatic adeno- or rhinovirus infections have been demonstrated to be more common among asthmatic patients (Macek et al., 1994, Malmstrom et al., 2006). Still, in our study, chronic respiratory condition did not associate with respiratory virus detection, which is rather surprising.

Among chronic non-respiratory conditions, cardiovascular diseases were more common in patients without respiratory symptoms and did not associate with respiratory viruses. This could be a result of the high prevalence of cardiovascular disease among Finns. Previously Lin et al. (2014) have shown among older people an association between influenza vaccination and a reduced risk of hospitalization due to stroke (Lin et al., 2014). In our study, heavier patients seemed to be more prone to influenza and parainfluenza virus infections. Zhang et al. (2013) have

suggested leptin mediating the pathogenesis of severe 2009 pandemic influenza A with a mouse model (Zhang et al., 2013). An association between body mass index and severe influenza-like illness has been reported (Cocoros et al., 2014). However, this association was shown among under-60-year-olds, and the respiratory viruses were not identified. Painter et al. suggest that obesity may impair vaccine-induced immunity and make obese adults more susceptible to influenza (Painter et al., 2015). Our study strengthens the idea that there could be an association with respiratory virus detection and patient´s weight and broadens it also to geriatric patients. Age did not associate with respiratory virus detection in our study.

In episodes without respiratory symptoms a respiratory virus was detected in 23%, which is in line with literature of patients from all age groups (Jartti et al., 2008). Interestingly, among these older patients, the number of bocavirus detections was low compared to the detections earlier reported among children. The number of RS viruses in co-detections was surprisingly high.

There have been no studies investigating bocavirus infections among older adults. We showed a low detection rate for this relatively newly discovered bocavirus 1. As there were no genuine acute bocavirus 1 infections, detections could be due only to short-term local replication or mere mucosal contamination of virus from grandchildren. Previous studies of adults have shown similar results (Fry et al., 2007, Garbino et al., 2009). These findings strengthen the idea that bocavirus 1 respiratory infection is more of a pediatric problem (Jartti et al., 2012).

The strengths of study I include prospective design, large sample size, inclusion of controls without respiratory symptoms, and sensitive virus-detection methods. In addition, bocavirus infections were serologically confirmed. There are also some limitations. The nasopharyngeal swab samples were collected from the upper airways, and thus infections solely in the lower airways may have been missed. The reference group of patients without respiratory symptoms was enrolled only during the first year of the 2-year study. Due to many chronic diseases in older adults, virus-induced respiratory symptoms may be difficult to distinguish from other symptoms. However, for dyspnea, we used an objective criterion based on oxygen saturation.

6.2 Virus findings and pneumonia

Study II showed three main findings: 1) pneumonia episodes were not associated with respiratory virus detection, 2) the indicators of severe bacterial infection, WBC count over 15 E9/L and CRP over 100 mg/L, were associated with pneumonia and 3) CRP over 100 mg/L was associated with death at the ward. In pneumonia episodes, the presence of a respiratory virus was not associated with short-term clinical outcomes, nor with WBC or CRP values. In all episodes with respiratory

symptoms, a detected virus was associated with a less severe clinical course in terms of fewer revisits.

In our cohort, 30% of older patients with pneumonia had a respiratory virus present in the nasopharynx, which is in line with the recent studies on adults that suggest that one-third of pneumonia cases are associated with a respiratory virus (Flamaing et al., 2003, Kobashi et al., 2001, Ruuskanen, 2011). We found rhinovirus to be the most common virus in pneumonia episodes, followed by coronavirus and influenza virus. Treanor et al. anticipated that the role of these common cold viruses, coronavirus and rhinovirus, among older patients would arise in the future, although today PIV, RSV and influenza are understood as the most harmful viruses among older people (Treanor & Falsey, 1999, van Asten et al., 2012, Han et al., 1999). Our findings support this idea of the rising significance of common viruses, especially the rhinovirus, among older adults (Treanor & Falsey, 1999, Atmar, 2005, Longtin et al., 2010). However, our analyses among this population showed no differences in severity of pneumonia episodes with or without a respiratory virus present, even though association between elevated disease severity and dual infection, especially rhinovirus/pneumococcal infection, in the adult population has been reported previously (Jennings, 2008, Burk et al., 2016).

In viral infections, frailty, immunologic weakening, and cardiopulmonary diseases are thought to predispose to pneumonia (Falsey, 2007). In our study of patients with respiratory symptoms, a respiratory virus was present in 40% of patients without pneumonia; the corresponding figure in patients with pneumonia was 30%. Moreover, in all episodes, the risk of a revisit seemed to be lower when a virus was detected. These findings fit the idea of respiratory viruses being most often only innocent bystanders in patients with pneumonia (Ruuskanen & Järvinen, 2014). We found that asthma and COPD were associated with shorter, under-2-week hospital episodes. This could be explained by effective, well-targeted drugs for these exacerbated chronic diseases.

We saw no difference in inflammatory markers according to virus etiology. We found that high CRP and WBC values are associated with pneumonia in patients with respiratory symptoms but have limited value as independent predictors for short-time prognosis, which is in line with literature (Engel et al., 2012). Previously, only relatively high CRP values have been shown to be useful in predicting the presence of pneumonia, and a cut-off value of 100 mg/L in adult populations is mentioned in a few studies (Blasi et al., 2010). In a relatively large CAPNETZ-study with 1337 patients aged 62 ± 18 years, Krueger et al. concluded that WBC count and CRP are higher in typical bacterial than in atypical or viral etiology community-acquired pneumonias (Krueger et al., 2009). However, Gao et al. showed that complement activation in patients infected with severe influenza A seems to correlate with high CRP levels (Gao et al., 2017).

Our data suggest that among older adults a respiratory disease elevating CRP over 100 mg/L could be linked to short-term mortality because pneumonia is more probable in such cases. Lee et al. showed similar results in their study with 424 patients aged 70.4 +/- 15.6 years with independent associations of both elevated CRP level and decreased albumin level to 28-day mortality (Lee et al., 2011). Also, Ortqvist et al. showed associations between disease severity and CRP but could not show association between high CRP and mortality in 203 hospital-treated pneumonia patients (Ortqvist et al., 1995). In the CAPNETZ-study mentioned above, Krueger et al. stated that both WBC and CRP were poor predictors of disease severity of community-acquired pneumonia (Krueger et al., 2009).

The strengths of study II include prospective design, large sample size and sensitive virus-detection methods. In addition, pneumonia was confirmed by a single study radiologist from chest x-rays with clear predefined criteria. There were some limitations also. We observed hospitalization-requiring episodes, and thus results cannot be generalized straight to treating older outpatients. The nasopharyngeal swab samples for virus analysis were collected from the upper airways and for this reason, infections solely in the lower airways may have been missed. Perhaps most importantly, due to common chronic diseases in older patients, respiratory symptoms caused by virus infection may be difficult to distinguish from other symptoms.

6.3 Prognostic tools in acute respiratory diseases among older adults

Study III with 289 older adult patients (mean age 83 years) had four main findings. First, hypoalbuminemia was associated with up to 5-year mortality after hospital stay. Second, 25(OH)D deficiency and hypoalbuminemia were common, being present in 59% and 55% of the study patients, respectively. Third, hypoalbuminemia was associated with pneumonia, dyspnea, over-13-night stay at ward and death at ward. Fourth, no associations were seen between serum 25(OH)D or LL-37 levels and long- and short-term clinical outcomes or disease severity. Associations between serum 25(OH)D, albumin or LL-37 levels and respiratory virus presences were not seen either.

More than half of our study patients had 25(OH)D deficiency. It is known that serum 25(OH)D acts as negative acute phase reactant, and this may explain to some extent low serum values measured during acute diseases (Waldron et al., 2013). Similar results have been seen in a Norwegian study with 241 community-acquired pneumonia survivors, with a high prevalence of 25(OH)D deficiency and inadequacy among hospitalized adults (Holter et al., 2016). In our study there was no difference

between serum 25(OH)D levels among patients with and without pneumonia, which could to some extent rule out the acute phase reactant effect. Holter et al. even suggested that 25(OH)D deficiency could be associated with long-term mortality. In addition, a South Korean study reported association between 25(OH)D concentration and 28-day all-cause mortality in 797 pneumonia patients with mean age 68.1 years (Kim et al., 2015). We tested these findings in our data, but no association with short-term or long-term outcomes could be seen; neither death at ward, revisit, nor over-13-night hospital stay associated with serum 25(OH)D level, and neither serum 25(OH)D level nor vitamin D supplement usage could be shown to associate with 1-, 2- or 5-year survival.

Serum albumin level below 3.5 g/dL among adults is defined as hypoalbuminemia. Defined like this, most of our study patients suffered from hypoalbuminemia. Hypoalbuminemia is known to associate with mortality and worse recovery after acute pathologies among older people (Cabrerizo et al., 2015, El-Solh et al., 2003, Liu et al., 2015). Serum albumin level decreases in infections (Soeters al., 2019). Our study is in line with both ideas. Hedlund et al. stated that community acquired-pneumonia patients with low serum albumin level should be observed and treated more intensively because a low serum albumin concentration was the most important factor independently associated with fatal disease in their study (Hedlund, 1995). Lee et al. showed in their study that the albumin level and CRP alone and together are associated with a 28-day mortality in hospitalized pneumonia patients with mean age 70.4 years (Lee et al., 2011). We had similar results. We showed associations between serum albumin level and pneumonia and higher CRP levels indicating more severe disease. Serum albumin level was even a clear prognostic factor of survival during 1-, 2- and 5-year surveillance time. Serum albumin level and age on admission were two independent factors that were prognostic regarding mortality up to 5 years. However, 5-year mortality was already associated with multiple factors, as one could expect. In addition to serum albumin, association with age, sex, other disease and the presence of respiratory virus was shown. We found that a respiratory virus detection on hospital admission was associated with better 5-year survival. As respiratory virus infections typically cause self-limiting illnesses, virus detection on admission could make more serious reasons for hospitalization less probable and this way give better 5-year survival prognosis.

Previous studies have suggested that production of LL-37 is well preserved among healthy older adults (Castañeda-Delgado et al., 2013). Our study confirms this idea as there was no association between LL-37 level and age in our study and therefore the production could be considered preserved with increasing age. There were no associations between LL-37 and long- or short-term clinical outcomes in our study. Disease severity describing CRP and WBC count were associated with serum LL-37 level, though. Guo et al reported that LL-37 may have predictive value

in 28-day survival among older sepsis patients (Guo et al., 2018). Our data with older pneumonia patients could not show similar association. Currie et al. have shown in vitro studies some antiviral activity of LL-37 against RSV, but we saw no associations between serum LL-37 level and virus presence overall or most prevalent single viruses, influenza virus, rhinovirus, or RSV (Currie et al., 2013). Elevated serum LL-37 levels in bacterial pneumonia compared with healthy subjects have also been reported (Majewski et al., 2018). However, we didn't see association between serum LL-37 level and pneumonia. LL-37 level was associated with serum CRP level and WBC count, though.

The strengths of study III include prospective design, relatively large sample size and long follow-up time. The study focused on serum 25(OH)D, albumin, and LL-37 levels in relation to each other and other common clinical tools, which bring the results closer to practice and give them concrete scale. Of course, there are also some limitations. The study does not take into account the seasonal circadian variation of vitamin D, and detailed nutritional status was not measured. As acute illness affects serum 25(OH)D and albumin levels acting as acute phase reactants, the results from this study may be usable only in treating patients with acute illness. The study observed hospitalization-requiring, often multimorbid, geriatric patients, and for this reason the results cannot be generalized as such to treating outpatients.

7 Summary/Conclusions

Conclusions below can be drawn from the present studies:

I Among older adults, the presence of respiratory viruses in the upper airways is only modestly associated with respiratory symptoms. Overweight status may increase the risk of respiratory viral infections. Chronic cardiovascular and respiratory diseases were not associated with virus detection. Influenza and rhinovirus were the most detected viruses among episodes with respiratory symptoms. The occurrence of acute metapneumovirus and bocavirus infections were low in older people.

II The detection of common respiratory viruses in the nasopharynx of older patients has limited value in assessing the severity of the disease or the short-term prognosis. Pneumonia should always be treated as a bacterial disease regardless of virus findings. Among older people, not one respiratory virus was associated with the presence, signs and symptoms, or prognosis of radiographically verified pneumonia. Serum CRP value over 80 mg/L and a WBC value over 15 E9/L indicated pneumonia, and a CRP over 100 mg/L was linked to elevated mortality during the hospital stay.

III It seems that serum albumin level on admission gives valuable information about the patients' long-term prognosis, general health and recovery potential in treating older patients with respiratory symptoms. At the same time, serum 25(OH)D and LL-37 levels don't seem to have long- or short-term prognostic value. Our finding underlines the importance of good nutritional status among older adults and shows the need for further studies to enlighten the possibly complex role of serum albumin in acute infections.

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