Diploma Thesis

Renal complications in severe PCR confirmed influenza A and B infections (sInfABInf) treated at intensive care units (ICU) in Styria between 2009 to 2021

by

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Declaration

I hereby declare that this thesis is my own original work and that I have fully acknowledged by name all of those individuals and organisations that have contributed to the research for this thesis. Due acknowledgement has been made in the text to all other material used. Throughout this thesis and in all related publications I followed the guidelines of "Good Scientific Practice".

Graz, 20th July 2023 Moritz Soffried m.p.

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Contents

Glossary

A

AKI Acute kidney injury. 4, 41, 42, 43
ALT Alanine transaminase. 18, 35
ARDS Acute respiratory distress syndrome. 21, 37
AST Aspartate transaminase. 18, 35

C

CKD Chronic kidney disease. v, vii, 5, 6, 7, 8, 24, 25, 26, 27, 28, 29, 31, 33, 35, 36, 38, 39, 40, 42, 43
CRP C-Reactive protein. 17, 35

G

GFR Glomerular filtration rate. 5

I

ICU Intensive care unit. 4, 7, 8, 12, 15, 26, 27, 33, 41, 42, 43

K

KDGIO Kidney Disease: Improving Global Outcome. v, 5, 8, 43

L

LDH Lactate dehydrogenase. 19, 36

N

NT-proBNP N-terminal prohormone of brain natriuretic peptide. vii, viii, 20, 36, 37

R

RNA Ribonucleic acid. 3

RRT Renal replacement therapy. 4, 23, 24, 43

RT-PCR Reverse transcription polymerase chain reaction. 3

S

sInfABInf severe PCR confirmed influenza A and B infections. vi, v, 7, 41, 42

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Zusammenfassung

Einleitung. Österreich besitzt im eruopäischen Vergleich eine der niedrigsten Impfraten gegen Influenza A und B, während gleichzeitig die Inzidenzrate von chronischen Nierenerkrankungen steigend ist. Gleichzeitig stellt eine chronische Nierenerkrankung einen signifikanten Risikofaktor für einen prognostisch ungünstigen Verlauf einer Influenza A Infektion dar. Unsere Studie verfolgt das wichtige Ziel, Aussagen über die Risikofaktoren im Kontext eines akuten Nierenversagens bei Behandlung auf einer Intensivstation zu finden und zu quantifizieren. Dazu analysieren wir die epidemiologisch vorhandenen Daten von Patienten, die mit einer PCR-bestätigten Influenza A oder B Infektion in der Steiermark auf einer Intensivstation behandelt wurden.

Methodik. Als Methodik wählen wir das Design einer retrospektiven Studie, wo wir klinische Daten sowie Laborparameter der Patienten und Patientinnen auswerten. Insgesamt analysieren wir 111 Patienten und Patientinnen. Die Basis dieser Studie fand auf der Datenerhebung von Matthias Funck statt, dessen Diplomarbeit "PCR confirmed influenza A and B infections treated at the intensive care unit of the Department of Internal Medicine of the Medical University of Graz between 2009 and 2020"einen kardiologischen Schwerpunkt betrachtet hat. In unserer Studie fokussieren wir uns insbesondere auf die Nierenfunktion.

Ergebnisse. In unserer restrospektiven Studie konnten wir zeigen, dass akutes Nierenversagen bei sInfABInf häufig vorkommt (in etwa 30 Prozent der Fälle), tendenziell mit einem erhöhten Letalitätsrisiko verbunden ist, aber die Aufenthaltsdauer auf der Intensivstation oder im Krankenhaus nicht verlängert.Akutes Nierenversagen trat besonders häufig bei Patienten mit vorbestehender Immunsuppression oder Herzinsuffizienz auf. Das C-reaktive Protein war bei Patienten mit akutem Nierenversagen tendenziell erhöht, was auf eine möglicherweise erhöhte Rate an schweren Sekundärinfektionen hinweist. Dieser Unterschied war jedoch nicht signifikant. Bei Patienten mit vorbestehender Niereninsuffizienz war die Dauer des Krankenhausaufenthalts während ihrer sInfABInf tendenziell länger als bei Patienten ohne vorbestehende Niereninsuffizienz.

Diskussion. Trotz aller Einschränkungen (geringe Patientenzahl, retrospektives Studiendesign, Lücken in der Erfassung der klinischen Daten mit teilweise unvollständiger klinischer Dokumentation) konnten wir zeigen, dass schwere Influenza-Infektionen nicht

nur zu schweren kardiopulmonalen, sondern auch zu relevanten renalen Komplikationen führen können. Weitere Forschung ist erforderlich, um diese wichtigen Fragen zu untersuchen. Patienten mit Niereninsuffizienz wird daher eine jährliche Grippeimpfung empfohlen.

Abstract

Introduction. Austria has one of the lowest vaccination rates against influenza A and B in Europe, while the incidence rate of chronic kidney disease is increasing. At the same time, chronic kidney disease is a significant risk factor for a prognostically unfavourable course of influenza A infection. Our study pursues the important goal of finding and quantifying statements about the risk factors in the context of acute kidney failure during treatment in an intensive care unit. For this purpose, we analyse the epidemiologically available data of patients who were treated with a PCR-confirmed influenza A or B infection an intensive care units in Styria.

Methods. As methodology we choose the design of a retrospective study, where we evaluate clinical data and laboratory parameters of the patients. In total, we analyzed 111 patients. The basis of this study was the data collection of Matthias Funck, whose diploma thesis "PCR confirmed influenza A and B infections treated at the intensive care unit of the Department of Internal Medicine of the Medical University of Graz between 2009 and 2020"considered a cardiological focus. In our study we focus especially on renal function.

Results. In our retrospective study, we were able to show that acute renal failure occurs frequently in sInfABInf (in approximately 30 percent of cases), tends to be associated with an increased risk of lethality, but does not prolong the length of stay in the intensive care unit or hospital. Acute renal failure was particularly common in patients with pre-existing immunosuppression or heart failure. C-Reactive Protein was tended to be elevated in patients with acute renal failure, indicating a possible increased rate of severe secondary infections. However, this finding was not significant. Patients with pre-existing renal insufficiency tended to have a longer length of hospital stay during their sInfABInf than patients without pre-existing renal insufficiency.

Discussion. Despite all limitations (small number of patients, retrospective study design, gaps in the collection of clinical data with partly incomplete clinical documentation) we could show that severe influenza infections can not only lead to severe cardiopulmonary but also to relevant renal complications. Further research is needed to investigate these important issues. Patients with renal insufficiency are therefore recommended to receive annual influenza vaccination.

Chapter 1

Introduction

1.1 Motivation

1.1.1 Vaccination rates and efficacy of vaccination

Influenza viruses are the most dangerous infectious agents in Europe, along with SARS-CoV-2, with reference to mortality rate per 100,000 population and disability adjusted life years. Elderly and comorbid patients are particularly at risk, with the highest mortality rate among patients requiring ICU treatment for influenza infection. [1]

Chronic kidney disease is an increasingly common comorbidity with age. These patients formally represent a relatively large influenza risk group. However, there are few detailed studies in the literature on chronic kidney disease and influenza mortality and morbidity risk.

There is also relatively little information on whether acute renal failure is frequently observed with severe influenza infection, whether this severe complication particularly affects patients with pre-existing chronic kidney disease, and whether it is associated with increased all-cause mortality.

While the Ministry of Social Affairs, Health, Care and Consumer Protection of Austria recommends the Influenza A and B vaccination each person who wants to gets vaccinated, especially children, adults over 60 years of age, chronically ill patients, and persons who work in health care institutions such as nursing homes or hospitals, Austria's vaccination rate for Influenza A and B remains one of the lowest in Europe

with under 10 percent of the population vaccinated in the 2011/2012 season. Among the elderly, only about 37 percent were vaccinated in 2011. [2, 3]

Nonetheless, scientific efficiacy of the Influenza vaccine in the scientific community is undisputed with efficiacy levels of about 48 percent compared to non-vaccinated individuals through all age groups. [4] It has also been shown that vaccination against Influenza A and B reduced all-caused mortality by about 20 percent in the elderly. Thus, vaccination of all population groups remains a preventive method for the prevention of death or serious illness caused by an Influenza A or B infection. [5]

1.2 Basics

1.2.1 The Kidneys

The kidneys are two bean shaped, paired organs, each approximately 12cm of length and are located in the retroperitoneum next to the collumna vertebralis approximately at projection to the eleventh and twelfth rib. [6] The smallest functioning unit of the kidney is the nephron and each kidney consists of about 1 million nephrons. No new nephrons can be formed and thus, the number of nephrons gradually decreases over life and with it, the physiological function of the kidney. Nephrons that were destroyed by inflammation or mechanical trauma cannot be restored, yet the remaining nephrons can adapt to allow for compensation. The renal corpuscule – also known as the Malphigi Body – consists oft he glomerolus and the Bowman's capsule. Blood is transported via the afferent arteriole into the glomerular capillaries, where the hydrostatic pressure forces the primary filtrate into the Bowman's capsule. The primary filtrate consists of electrolytes, fluids, amino acids as well as small molecules, some of which are reabsorbed into the peritubular capillaries. Other molecules might get secreted into the proximal tubule. The kidney also serves an important function in acid-base-equilibrium, being one of only two maintaining factors of a regulated pH, the other one being of respiratory nature, by producing or excreting hydrogen ions as well as bicarbonate ions. The kidneys function in erythropoiesis is also pivotal, secreting erythropoietin, a hormone and glycoprotein, which promotes maturation and formation of erythrocytes. Blood pressure is also regulated closely by the kidney by producing and secreting aldosterone in response to low blood pressure as well a slow blood volume. [7]

1.2.2 Influenza Virus

Influenza, a negative sense, single-stranded RNA virus, belongs to the family of Orthomyxoviridae (coming from the Greek word myxa, meaning mucus), consisting of three distinguishable types: A, B and C. [8]

Influenza A virus subtype has the highest pathogenicity among influenza viruses. Typical symptoms include rhinitis, pharyngitis, fever, and limb and muscle pain. Involvement of the lower respiratory tract is considered to have an unfavorable prognosis, and dangerous courses can occur if the central nervous system and internal organs are involved.[9] Influenza A virus can also be classified using two important surface glycoproteins, called hemagglutinin and neuraminidase. While hemagglutinin is responsible for smuggling the virus into the cell and thus needed to initiate infection, neuraminidase is responsible for transporting the virus out of the cell. There are 18 hemagglutinin subtypes and 11 neuraminidase subtypes currently known. [10] Influenza B infections are typically somewhat milder but are clinically indistinguishable from other influenza subtype infections. [9]

Influenza C viruses can be distinguished and detected microbiologically, but they are only mildly pathogenic and run a very mild course, which is why they play only a minor role in everyday clinical practice.[9]

Diagnostically, influenza infection is detected by enzyme immunoassays as well as hemagglutination tests, the viral RNA itself can be detected by RT-PCR, the viruses themselves can be isolated in chicken embryos as well as cell cultures.[9]

Therapeutically, influenza infection is treated with zanamivir or oseltamivir, which inhibit neuraminidase activity and thus prevent further release of viruses from the cell. [9]

1.2.3 History of Influenza Infections

The first confirmed influenza pandemic took place in 1580, where influenza came to Europe from Asia via Africa and the pandemic lasted about 6 months. Between 1700 and 1830 there are 9 reported pandemics. The most serious pandemic took place from 1918 to 1920, which is synonymous called the Spanish flu. Records include statements such as "the pandemic ranks with the plague of Justinian and the Black Death as one

of the three most destructive human epidemics"[11] According to various estimates, up to 50 million people died during this period as a direct result of influenza infection, while about one third of the world's population was infected at some point between 1918 and 1920. [12]

1.2.4 Acute Kidney Injury

AKI is classified by the RIFLE Criteria and is either defined by elevation from baseline serum creatinine as well as the partial or complete loss of urinary output over a defined period of time. For this classification, one should always use the worst available parameter.[13]

Class	Glomerular filtration rate criteria	Urine output criteria
Risk	Serum creatinine × 1.5	< 0.5 ml/kg/hour × 6 hours
Injury	Serum creatinine × 2	< 0.5 ml/kg/hour × 12 hours
Failure	Serum creatinine × 3, or serum creatinine ≥ 4 mg/dl with an acute rise > 0.5 mg/dl	< 0.3 ml/kg/hour × 24 hours, or anuria × 12 hours
Loss	Persistent acute renal failure = complete loss of kidney function > 4 weeks	
End-stage kidney disease	End-stage kidney disease > 3 months	

Figure 1.1: RIFLE Criteria [14]

Acute kidney injury is common in the hospital, with around 20 per cent of admitted patients affected. Known Risk factors include diabetes, haematological malignancies and infections. The underlying reason for AKI can be found pre-renal, renal, or post-renal. Pre-renal reasons for AKI can be hypovolaemia by any reason, hypotension including low cardiac output or a combination of these factors. Renal reasons for AKI include acute tubular necrosis, which is also the most common underlying disease for renal acute kidney failure. It is important to note, that almost all reasons for pre-renal acute kidney injury will lead to acute tubular necrosis when left untreated. Postrenal renal failure is usually caused by a drainage obstruction in the lower urogenital tract, such as kidney stones or urothelial tumours. Management of Acute kidney injury include fluid balance, management and correction of electrolyte disturbances as well as measurement of urinary output.[15] It is recognized as a major threat to patients outcomes especially when patients were admitted to the ICU and underwent RRT. Of all admitted ICU patients, almost 40 percent developed AKI at some point during their admission to the ICU. Hospitality mortality remains very high with almost 33 percent of people dying that were diagnosed with AKI [16, 17]

1.2.5 Chronic Kidney Disease

Chronic kidney disease is a term to describe lost renal function over a longer period of time (usually over 3 months). Reasons for CKD include congenital or inherited disease such as polycystic kidney disease, oxalosis or congenital obstructive uropathy. Glomerular disease, including primary or secondary glomerular disease such as diabetes, vascular disease such as hypertension or vasculitis, tubulointerstitial disease and urinary tract obstruction. CKD is a globally prevalent condition with substantial variation in incidence rates across populations. The incidence increases with age, with a higher prevalence observed in older individuals. Estimates suggest that approximately 10 percent of the global population is affected by CKD. However, the true burden of the disease may be underestimated due to undiagnosed cases. Certain populations, such as those with diabetes or hypertension, are at a higher risk of developing CKD. CKD affects approximately 30 percent of the adult population over 85 years of age, which makes it a significant disease in terms of prevalence.[15] CKD can be classified using the KDGIO 2021 clinical practice guideline for the evaluation and management of CKD, which uses GFR and Albumin:Creatinine ratio. [18]

Risk for Chronic Kidney Disease by GFR and albuminuria categories				Protein in Urine Albumin to Creatinin Ratio (mg/g Crea or mg/mmol Crea)		
				normal to midly increased < 30 mg/g < 3 mg/mmol	moderately increased 30 - 300 mg/g 3 - 30 mg/mmol	severely increased > 300 mg/g > 30 mg/mmol
GRF Glomerular Filtration Rate ml/min/1.73 m² milliliters of fluid filtered through the kidney per minute normalized to an average body surface area	G1	normal and high	≥ 90	low risk	increased risk	high risk
	G2	mild reduction	60-89	low risk	increased risk	high risk
	G3a	mild to moderate reduction	45-59	increased risk	high risk	very high risk
	G3b	moderate to severe reduction	30-44	high risk	very high risk	very high risk
	G4	severe reduction	15-29	very high risk	very high risk	very high risk
	G5	kidney failure	< 15	very high risk	very high risk	very high risk

Figure 1.2: KDGIO Classification of chronic kidney disease [19]

Complications of Chronic kidney disease include anaemia, endocrine disorders, mineral and bone disorder, and cardiovascular disease. Chronic kidney disease patients are

about 16 times more likely to develop cardiovaskular disease compared to the healthy population. Rare but severe complications include nephrogenic systemic fibrosis and calciphylaxis. Prevention of progressive Chronic kidney disease and retention of kidney function is key in management of patients with Chronic kidney disease [15]

Chapter 2

Materials and Methods

2.1 Methods

For this study we used in part data previously acquired by Matthias Funck. To be able to answer the question of renal complication in sInfABInf we expanded on the data by adding different laboratory values and calculating different statistical outcomes. These are explained in detail below.

2.1.1 Study objectives

Chronic kidney disease has a long lasting impact upon patients, especially when patients suffering from CKD acquire another serious illness. Our study has three main objectives:

1. To determine the epidemiological, clinical and laboratory characteristics of patients with and without pre-existing Chronic kidney disease treated for sInfABInf on ICU in Styria.

2. To determine the outcome of patients with and without pre-existing Chronic kidney disease treated for sInfABInf on ICU in Styria.

3. To determine the long-term deterioration of renal function due to an episode of sInfABInf, comparing the renal function in the two years bevor and the two years after the sInfABInf.

2.1.2 Study design

Our study is a retrospective study with PCR confirmed influenza A and B infections and patients were treated on different ICU in Styria (most cases at the medical university of Graz). This study was conducted by the department of pulmonology in cooperation with the department of nephrology as well as the department of infectious diseases at the medical university of Graz.

It included the years between 2009 and 2020. Altogether five influenza seasons were covered, which are 2009/10, 2016/17, 2017/18, 2018/19 and 2019/20. During this period, 111 patients with PCR-confirmed influenza infections and their treatment on ICU were analyzed. RIFLE Criteria were deemed as fulfilled if patients scored at least 2 or greater, considered injury according to the RIFLE Criteria. Overall, 32 patients developed renal complications during their ICU treatment.

For patients with preexisting CKD, we used the KDGIO classification, based only on Glomerular Filtration rate. Albuminuria was not available for the majority of the patients and we thus decided to only rely on Glomerular Filtration rate. We did not differentiate between stages 3A and 3B when classifying CKD

For statistical analysis we used chi-square-test, as well as fisher exact test.

2.2 Data collection

This study expands upon the data collected by Matthias Funck for his diploma thesis called "PCR confirmed influenza A and B infections treated at the intensive care unit of the Department of Internal Medicine of the Medical University of Graz between 2009 and 2020". In this work he focused on cardiovascular/pulmonary complications. We expand it upon the data of kidney function and classifies according to KDGIO Guidelines for Kidney Injury. Patient data was collected anonymously by Matthias Funck and ethic approval was granted by the local ethic committee based upon 23-049 ex 10/11 and associated amendments. (Date 19.05.2020).

Chapter 3

Results

3.1 Acute renal failure and renal complication

3.1.1 Demographic Data

Age distribution and gender differences in development of renal complication

We had an overall of 111 patients. 32 patients had renal complication. 20 patients were male and had had renal complication. 12 patients were female and had renal complication. 75 patients were male and had no had renal complication. 5 patients were female and had no renal complication.

Median age of the patient population was 66 years (IQR 56.5 - 75.5). Median age of male patients with renal complication was 71 years (IQR 62 - 76). Median age for woman with renal complication was 22 years (IQR 12.5 - 49.5). Median age for males without renal complication was 65 years (IQR 54.25 - 74.75). Median age for woman without renal complication was 58 years (IQR 48 - 62).

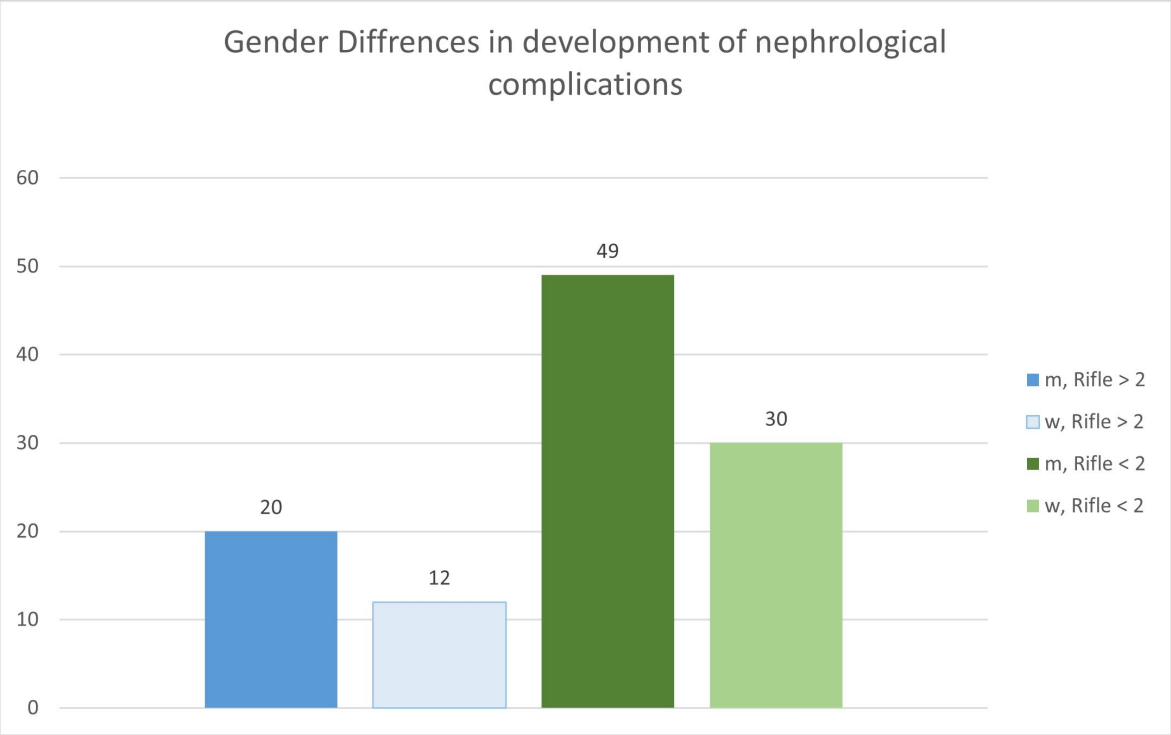

Figure 3.1: Gender Differences, RIFLE $< 2 = 0$ - 1, RIFLE $> 2 = 2$ - 5

3.1.2 Hospitalization

Median Hospital Stay

All patients included in this study were hospitalized and treated in a hospital in the federal state of Styria. Median hospital stay was 14 days (IQR 8.5 - 25.5) throughout both patients groups. The median hospital stay for the patient group without development of renal complication was also 14 days (IQR 8 - 23). The median hospital stay for the patient group with development of renal complication was 14.5 days (IQR 9 - 29).

ICU Stay

Median ICU stay for all patients was 6 days (IQR 3 - 13). For the patient group with development of renal complication, the median ICU stay was 6.5 days (IQR 4 - 14) and for the patient group without renal complication it was 6 days (IQR 3 - 13).

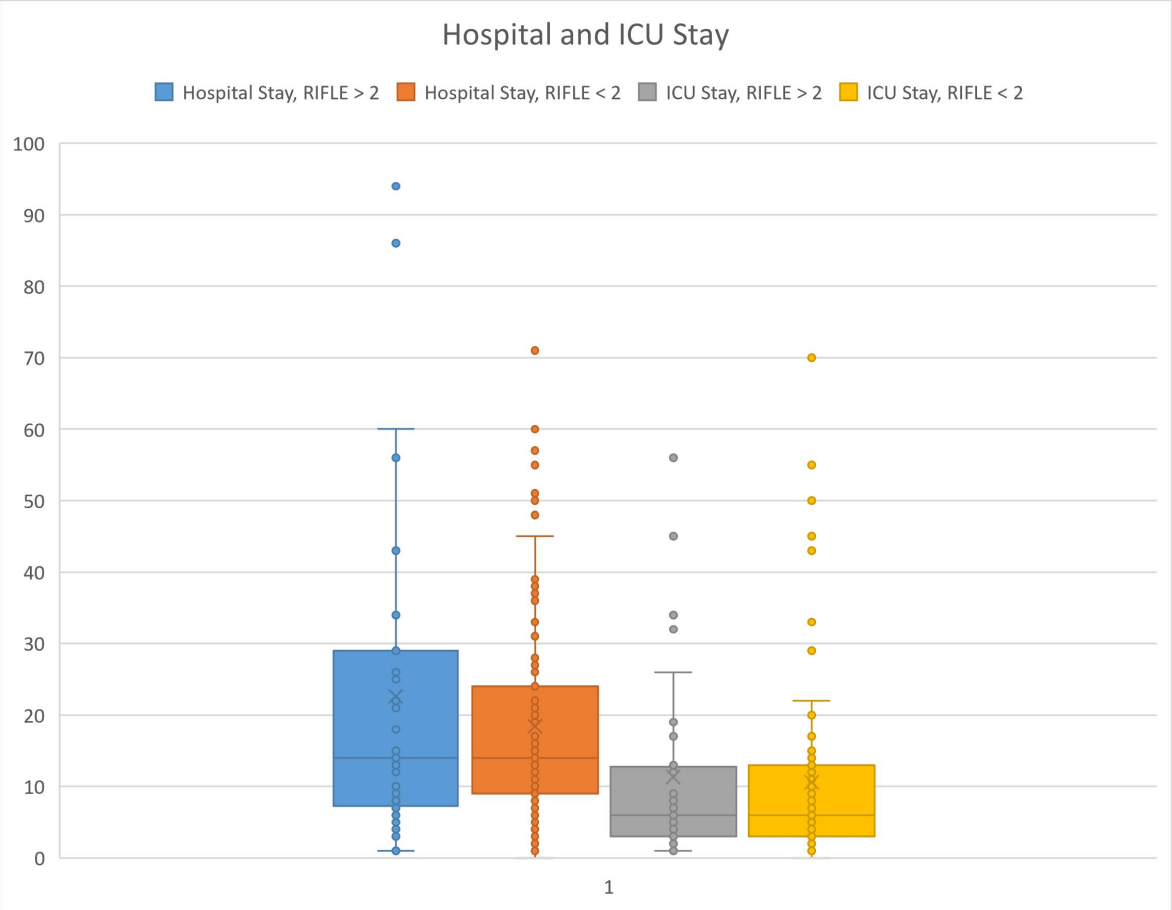

Figure 3.2: Hospital Stay, RIFLE $< 2 = 0$ - 1, RIFLE $> 2 = 2$ - 5

3.1.3 Clinical Presentation

Shortness of Breath

Shortness of Breath was observed in 78 patients. In the patient group with renal complication, 5 patients had shortness of breath, while 73 patients who had no renal complication suffered also from shortness of breath.

Diarrhea

Diarrhea was observed in an overall of 6 patients. In the patient group with renal complication, 0 patients had diarrhea, while 6 patients who had no renal complication had diarrhea.

Nausea / Vomiting

Nausea or vomiting was observed in 11 patients. 1 patient suffered renal complication and also nausea or vomiting. 10 patients had no renal complication and suffered from nausea or vomiting.

Myalgia

Myalgia was observed in 7 patients. 0 patients had renal complication and myalgia, while 7 patients had myalgia and no renal complication.

3.1.4 Vital Parameters

ICU Admission Temperature

We observed ICU admission Temperature in an overall of 101 patients. Median admission temperature was 37.6 (IQR 36.8 - 38.4). From all patients with renal complication, in 30 patients body temperature at ICU admission was available. Their median admission temperature was 37.8 (IQR 36.3 - 38.3). From all patients without renal complication, in 71 patients body temperature at ICU admission was available. Their median admission temperature was 37.5 (IQR 36.9 - 38.4).

Blood Pressure

Systolic blood pressure was recorded for 108 out of 111 patients. Systolic blood pressure was not measured in only three patients within the group of patients who did not develop a renal complication. Median systolic blood pressure for all patients was 120 mmHg (IQR 99.75 - 150). From all patients with renal complication, in 30 patients blood pressure at ICU admission was available. 30 patients developed renal complication, their median systolic blood pressure was 117 mmHg (IQR 95 - 134). From all patients without renal complication, in 78 patients blood pressure at ICU admission was available. Their median systolic blood pressure was 122 mmHg (IQR 102.75 - 150.5).

3.1.5 Laboratory Values

Leukocytes

We recorded leukocyte levels in every patient. The leukocyte counts fell within a normal range of 4.4 to 11.3 x10^9/L. Counts below 4.4 x10^9/L were classified as leukopenia, while counts above 11.3 x10^9/L were categorized as leukocytosis. The median leukocyte count of all patients was 8.52. (IQR 6.11 - 11.98). Median leukocyte count of the patient group with the occurrence of a renal complication was 9.54 (IQR 6.48 - 10.65). Median leukocyte count of the patient group without renal complication was 8.72 (IQR 5.92 - 12.60).

		Total	Patients with renal complications	Patients without renal Complications	Significance
		N=111	N= 32	N = 79	
	Leukopenia	17	3	14	
Leukocytes	Normal	62	21	41	0.3997
	Leukocytosis	32	8	24	

Table 3.1: Leukocytes

Neutrophile Granulocytes

The percentage of neutrophil granulocytes among the leucocytes was a median of 84 per cent in all patients. (IQR 77 - 90). In patients with renal complication, the percentage was 88.5 (IQR 83.75 - 90.25). In patients without renal complication, the percentage was 82 (IQR 76 - 88).

Hemoglobin and Hematocrit

In all patients, hemoglobin and hematocrit levels were assessed. Normal hemoglobin levels for men ranged from 13.0 to 17.5 g/dL, while for women, they ranged from 12.0 to 15.3 g/dL. Hemoglobin levels below 13.0 g/dL in men and below 12.0 g/dL in women indicated anemia. Conversely, hemoglobin levels exceeding 17.5 g/dL in men and 15.3 g/dL in women indicated elevated hemoglobin levels.

Normal hematocrit levels for men ranged from 40 percent to 50 percent, while for women, they ranged from 35 percent to 45 percent. Hematocrit levels below 40 percent

in men and below 35 percent in women indicated low hematocrit levels, whereas levels exceeding 50 percent in men and 45 percent in women indicated high hematocrit levels.

The median hemoglobin in all patients was 12.50 g/dL (IQR 10.15 - 14.75). In the patient group with renal complication, the median hemoglobin was 11.60 g/dL (IQR 9.80 - 13.73). In the patient group without renal complication, the hemoglobin was 13.30 g/dL (IQR 10.95 - 14.95).

		Total	Patients with renal complications	Patients without renal Complications	Significance
Hemoglobin		N=111	N= 32	N = 79	0.2757
	Low	53	19	34	
	Normal	54	12	42	
	High	4	1	3	
Hematocrit		N=111	N= 32	N = 79	0.6226
	Low	61	20	41	
	Normal	45	11	34	
	High	5	1	4	

Table 3.2: Hemoglobin and Hematocrit

Platelet Counts

Platelet counts within the range of 140-440 x10^9/L were deemed normal. Counts below 140 x10^9/L indicated thrombocytopenia, while counts exceeding 440 x10^9/L indicated thrombocytosis.

The median platelet count was 188 G/l (IQR 131 - 225) in all patients. In patients with renal complication, this was 201.19 G/l (IQR 132 - 220.5). In patients without renal complication, the median platelet count was 190 G/l (IQR 131 - 226.5).

		Total	Patients with renal complications	Patients without renal Complications	Significance
Platelet Count		N=111	N= 32	N = 79	0.3370
	Thrombopenia	32	10	22	
	Normal	76	20	56	
	Leukocytosis	3	2	1	

Table 3.3: Platelet count

Creatinine Levels

In all patients, creatinine levels on hospital admission were assessed. On ICU Admission, 109 patients were assessed. Normal creatinine levels were up to 1.20 mg/dL in men and up to 1.00 mg/dL in women. Creatinine levels exceeding 1.20 mg/dL in men and 1.00 mg/dL in women were considered elevated.

The median creatinine concentration on the day of admission of all patients was 1.15 mg/dl (IQR 0.88 - 1.72). The median creatinine concentration of all patients with renal complication was 1.70 mg/dl (IQR 1.15 - 3.67). The median creatinine concentration in patients without renal complication was 1.04 mg/dl (IQR 0.8 - 1.52).

The median creatinine concentration on ICU admission was 1.11 mg/dl (IQR 0.89 - 1.81) The median creatinine concentration of all patients with renal complication on ICU admission was 1.77 mg/dl (IQR 1.07 - 3.64) The median creatinine concentration of all patients without renal complication on ICU admission was 1.07 mg/dl (IQR 0.80 - 1.41)

		Total	Patients with renal complications	Patients without renal Complications	Significance
Creatinine Adm.		N=111	N= 32	N = 79	
	Normal	56	9	47	
	Elevated	55	23	32	0.0034
Creatinine ICU		N=109	N= 32	N = 77	
	Normal	58	9	49	
	Elevated	51	23	28	0.0007

Table 3.4: Creatinine Counts

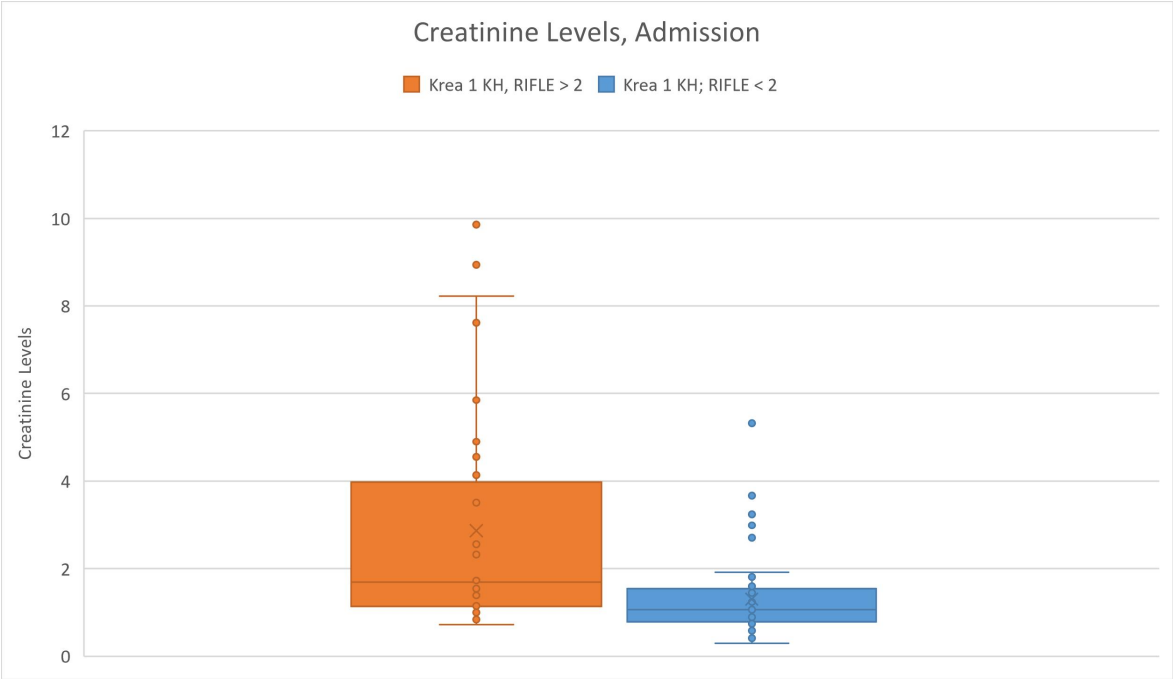

Figure 3.3: Creatinine Levels on Admission, RIFLE $< 2 = 0$ - 1, RIFLE $> 2 = 2$ - 5

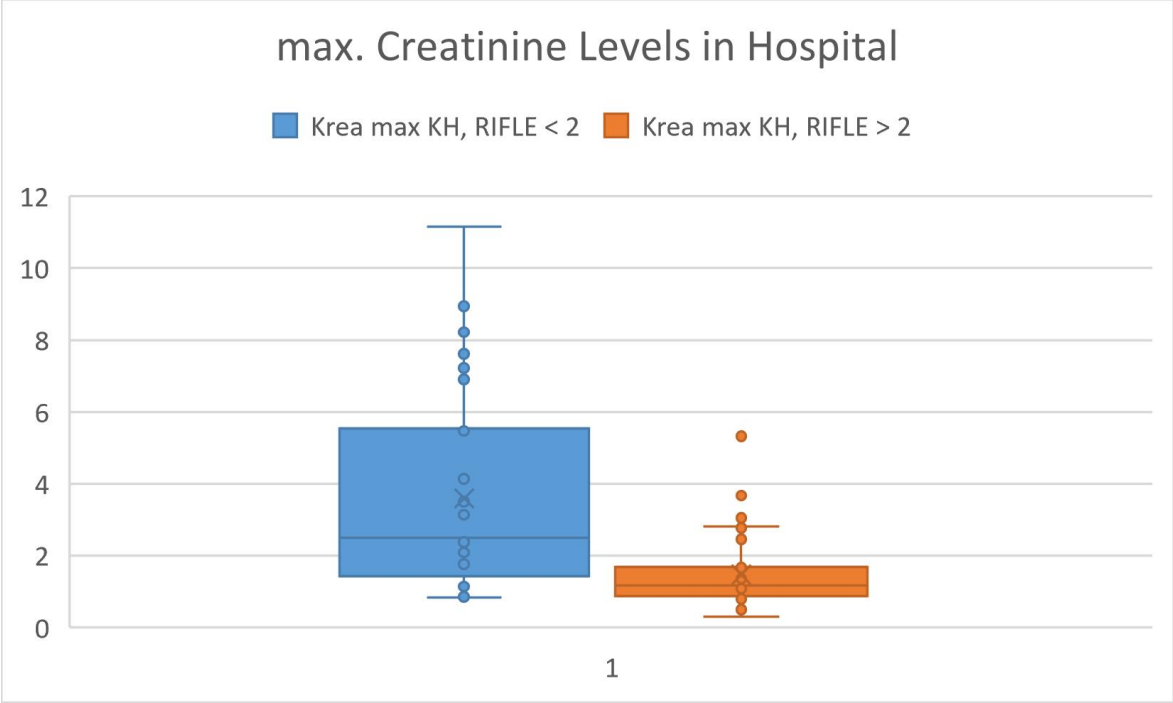

Figure 3.4: Maximum Level of Creatinine during hospital stay, RIFLE $< 2 = 0$ - 1, RIFLE $> 2 = 2$ - 5

C-Reactive protein

C-Reactive protein levels were measured in all patients. Normal CRP levels were up to 5 mg/L, while levels above 5 mg/L were considered elevated.

The median CRP concentration was 93.50 mg/l (IQR 34.20 - 197.55). In patients with renal complication, the median CRP concentration was 159.89 mg/l (IQR 50.03 - 250.68). In patients without renal complication, the median CRP concentration was 79.90 mg/l (IQR 31 - 179.60).

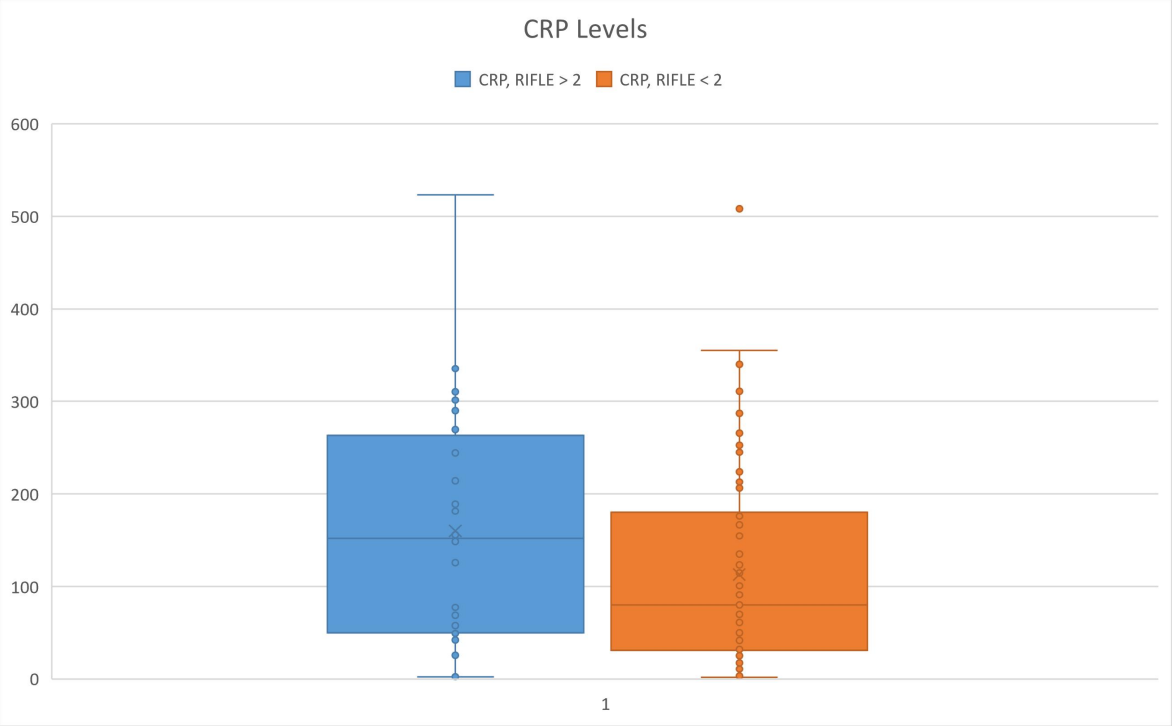

Figure 3.5: C-Reactive Protein Levels, RIFLE $< 2 = 0$ - 1, RIFLE $> 2 = 2$ - 5

		Total	Patients with renal complications	Patients without renal Complications	Significance
CRP		N=111	N= 32	N = 79	
	Normal	6	3	3	
	Elevated	105	29	76	0.3523

Table 3.5: C-reactive Protein

Aspartate transaminase and Alanine transaminase Levels

AST levels were assessed in all patients. Normal AST levels were up to 50 U/L in men and up to 35 U/L in women. AST levels exceeding 50 U/L in men and 35 U/L in women were considered elevated. The normal and elevated levels for ALT were the same as for AST levels.

The median AST concentration in all patients was 48 U/l (IQR 33 - 93.25). In patients with renal complication, the median AST concentration was 66.59 U/l (IQR 23.75 - 70.50). In patients without renal complication, the median was 79.90 U/l (IQR 31 - 179.60).

The median ALT concentration in all patients was 26 U/l (IQR 18.25 - 44). In patients with renal complication, the median ALT concentration was 40.56 U/l (IQR 18.75 - 44.75). In patients without renal complication, the median was 25.5 U/l (IQR 18.25 - 44).

		Total	Patients with renal complications	Patients without renal Complications	Significance
		N=110	N= 32	N = 78	
	Normal	55	15	40	
AST	Elevated	55	17	38	0.8340
		N=110	N= 32	N = 78	
	Normal	82	22	60	
ALT	Elevated	28	10	18	0.4701

Table 3.6: AST and ALT Levels

Bilirubin

Bilirubin levels within the range of 0.10 - 1.20 mg/dL were considered normal. Levels exceeding 1.20 mg/dL were classified as hyperbilirubinemia.

The median bilirubin concentration in all patients was 0.47 mg/dl (IQR 0.29 - 0.87). In patients with renal complication, the median bilirubin concentration was 0.83 mg/dl (IQR 0.25 - 0.81). In patients without renal complication, the median bilirubin concentration was 0.5 mg/dl (IQR 0.3 - 0.87).

		Total	Patients with renal complications	Patients without renal Complications	Significance
		N=107	N= 31	N = 76	
	Normal	91	27	64	
Bilirubin	Elevated	80	26	54	1

Table 3.7: Bilirubin

Lactate dehydrogenase Levels

Normal LDH levels were determined to be between 120 and 240 U/L. LDH levels above 240 U/L were considered elevated. The median LDH concentration in all patients was 316 U/l (IQR 245.75 - 480.75). In patients with renal complication, the median LDH concentration was 513.29 (IQR 216.5 - 443). In patients without renal complication. the median LDH concentration was 294 U/l (IQR 240 - 518).

		Total	Patients with renal complications	Patients without renal Complications	Significance
		N=104	N= 31	N = 73	
	Normal	24	5	19	
LDH	Elevated	80	26	54	0.3193

Table 3.8: Lactate Dehydrogenase Levels

Troponin T Levels

Normal Troponin T levels were defined as up to 14 pg/mL. Levels exceeding 14 pg/mL were considered elevated Troponin T levels.

The median troponin T concentration in all patients was 50 pg/ml (IQR 31 - 96.75). In patients with renal complication, the median troponin T concentration was 72.38 pg/ml (IQR 36 - 55). In patients without renal complication, the median troponin T concentration was 57.5 pg/ml (IQR 27.75 - 107).

		Total	Patients with renal complications	Patients without renal Complications	Significance
		N=50	N= 16	N = 34	
	Normal	4	1	3	
Troponin T	Elevated	46	15	31	1

Table 3.9: Troponin T Levels

N-terminal prohormone of brain natriuretic peptide Levels

Normal NT-proBNP levels were defined as up to 150 pg/mL in women and up to 100 pg/mL in men. Levels exceeding 150 pg/mL in women and 100 pg/mL in men were considered increased NT-proBNP levels. The median NT-proBNP concentration in all patients was 2713 pg/ml (IQR 788.98 - 10709.5). In patients with renal complication, the median NT-proBNP concentration was 18793 pg/ml (IQR 5834.5 - 18405.25). In patients without renal complication, the median NT-proBNP concentration was 1966 pg/ml (IQR 276.5 - 3859).

		Total	Patients with renal complications	Patients without renal Complications	Significance
		N=43	N= 12	N = 31	
	Normal	3	0	3	
NT-proBNP	Elevated	40	12	28	0.5478

Table 3.10: NT-proBNP Levels

3.1.6 Blood Gas Analysis

Arterial pO_2, arterial pCO_2, pH and HCO_3 levels were measured for blood gas analysis and the Horovitz index H was calculated:

$$H = \frac{\text{arterial p}O_2}{F_iO_2} \tag{3.1}$$

Normal levels for arterial pO_2 were considered to be between 71 and 104 mmHg. Levels below 71 mmHg were classified as hypoxemic, while levels above 104 mmHg were classified as hyperoxemic. Arterial pO_2 levels were available for 108 out of 111 patients.

Arterial pCO_2 levels within the range of 35-45 mmHg were considered normocapnic. Levels below 35 mmHg were classified as hypocapnic, while levels above 45 mmHg were classified as hypercapnic. It should be noted that arterial pCO_2 levels were not available for 3 patients. [20]

For arterial pH, levels ranging from 7.350 to 7.450 were considered normal. Levels below 7.350 were classified as acidosis, while levels above 7.450 were classified as alkalosis.[20] pH levels were available for 109 out of 111 patients.

HCO_3 levels within the range of 21 to 26 mmol/L were considered normal. Levels below 21 mmol/L were classified as decreased HCO_3 levels, while levels above 26 mmol/L were classified as elevated HCO_3 levels.[20] HCO_3 levels were available for 102 out of 111 patients.

The Horovitz index was calculated by dividing the arterial pO_2 by the fraction of oxygen in the inhaled air (F_iO_2). Normal levels were considered to be above 300. Levels between 200 and 300 were classified as mild ARDS, levels between 100 and 200 as moderate ARDS, and levels below 100 as severe ARDS, according to the Berlin definition. [21]

Median F_iO_2 levels were 0.50 for all patients. (IQR 0.37 - 0.61). Median F_iO_2 levels for Patients with development of renal complication were 0.41 (IQR 0.36 - 0.60). Median F_iO_2 for patients without renal complication was 0.50 (IQR 0.37 - 0.70).

		Total	Patients with renal complications	Patients without renal complications	Significance
arterial pO_2		N=108	N= 32	N = 76	
	Hypoxemic	39	13	26	
	Normoxemic	38	13	25	0.3482
	Hyperoxemic	31	6	25	
arterial pCO_2		N=108	N= 31	N = 77	
	Hypocapnic	34	11	23	
	Normocapnic	25	7	18	0.8247
	Hypercapnic	49	13	36	
pH		N=109	N= 31	N = 78	
	Acidosis	49	15	34	
	Normal	30	10	20	0.4705
	Alkalosis	30	6	24	
arterial HCO_3		N=102	N= 31	N = 71	
	Decreased	30	10	20	
	Normal	32	11	21	0.6592
	Elevated	40	10	30	
Horowitz Index		N=107	N= 32	N = 75	
	Severe LI	15	6	9	
	Moderate LI	42	10	32	0.5956
	Mild LI	32	11	21	
	No LI	18	5	13	

Table 3.11: Blood Gas Analysis

3.1.7 Past Medical History - Underlying Disease

Asthma

We observed Asthma in a total of 3 patients. 0 Patients with Asthma had renal complication, while 3 patients had no renal complication.

COPD

We observed COPD in a total of 38 patients. 9 Patients with COPD had renal complication, while 29 patients had no renal complication.

Smoking

We observed a smoking habit in 28 patients. 8 patients had renal complication while 20 had no renal complication.

Coronary heart disease

We observed coronary heart disease in 25 patients. 9 patients had renal complication while 16 had not.

Congestive heart failure

We observed congestive heart failure in 30 patients. 13 patients had renal complication while 17 had no renal complication.

Arrythmia

We observed arrythmia, including all entities and origins, in 32 patients. 15 had renal complication while 17 patients had no renal complication.

Arterial Hypertonus

We observed arterial hypertonus in 60 patients. 19 Patients had renal complication while 41 had no renal complication.

Diabetes Mellitus Type 2

We observed diabetes mellitus type 2 in 18 patients. 7 patients had renal complication while 11 had no renal complication.

Malignancies

We observed malignant tumors in 20 patients. 5 patients had renal complication while 15 had no renal complication.

Immunosuppression

We observed immunosuppression in 15 patients. 9 patients had renal complication while 6 had no renal complication.

Prehospital RRT

We observed prehospital Renal replacement therapy in 10 patients. 9 patients had renal complication while 1 had no renal complication.

Intrahospital RRT

We observed intrahospital Renal replacement therapy 18 patients. 17 patients had renal complication while 1 had no renal complication.

Disease	Total N=111	Patients with renal complications N=32	Patients without renal complications N=79	Significance
Asthma	3	0	3	0.5555
COPD	38	9	29	0.5085
Smoker	28	8	20	1
Coronary Heart Disease	25	9	16	0.4526
Heart Failure	30	13	17	0.0582
Arrythmia	32	15	17	0.0109**
Arterial Hypertension	60	19	41	0.5321
Diabetes Mellitus Type 2	18	7	11	0.3938
Malignancies	20	5	15	0.7896
Immunosuppression	15	9	6	0.0109**
prehospital RRT	10	9	1	0.0001**
intrahospital RRT	18	17	1	0.0001**

Table 3.12: Underlying Disease

Mortality and Death

Out of 32 patients with development of renal complications, 15 survived their illness and 17 patients died during their hospital stay. In the patient group without renal complications, 52 patients survived and 27 succumbed to their illness. This finding was not statistically significant. (p=0.0866)

3.2 Severe Influenza in patients with preexisting chronic kidney disease

Out of all 111 analyzed patients, 81 had no preexisting CKD while 30 patients had preexisting CKD.

3.2.1 Demographic data

Age

Median age for patients with preexisting CKD was 71.5 years (IQR 63 - 77.75), while median age for patients without preexisting CKD was 63 years (IQR 54 - 73).

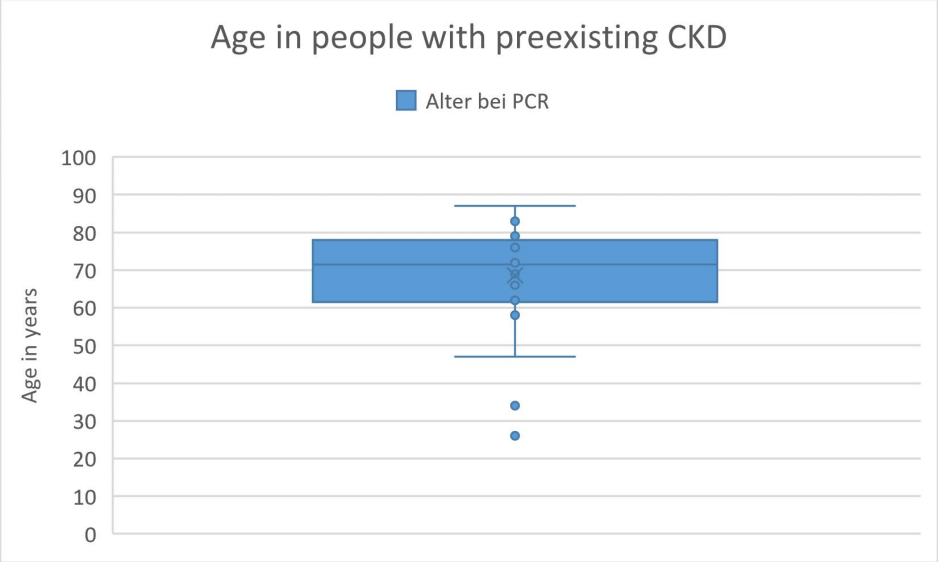

Figure 3.6: Age of patients with preexisting CKD.

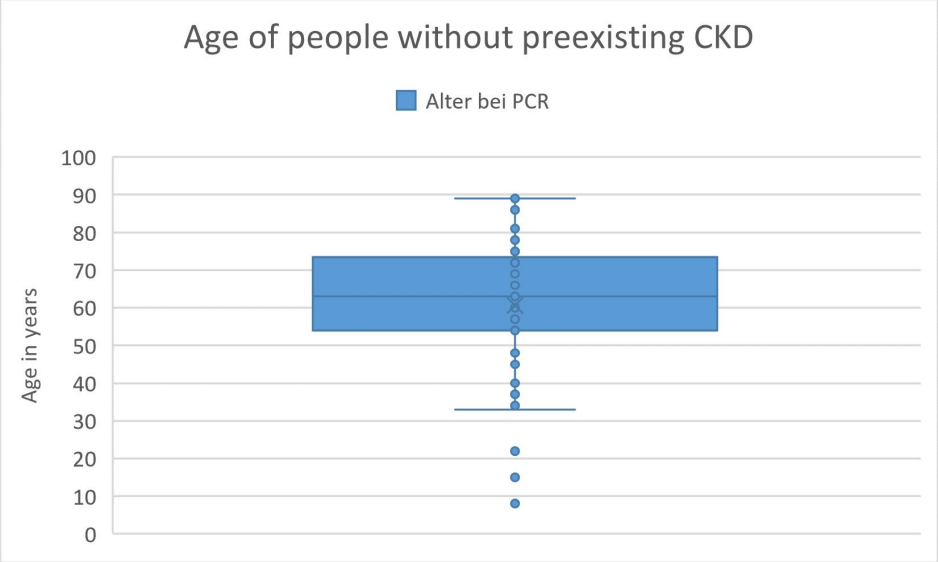

Figure 3.7: Age of patients without preexisting CKD.

Gender differences

Of all 81 patients with no known preexisting CKD, 28 patients were male, while 53 patients were female. Out of all 30 patients with preexisting CKD, 14 were female while 16 were male.

3.2.2 Hospitalization

Hospital stay

In the patient group with preexisting CKD, the median hospital stay was 17.5 days (IQR 9.25 - 28.5). In the patient group without preexisting CKD, the median hospital stay was 13 days (IQR 8 - 22).

ICU stay

In the patient group with preexisting CKD, the median ICU stay was 6 days (IQR 3 - 12.75). In the patient group without preexisting CKD, the median ICU stay was 6 days (IQR 3 - 13).

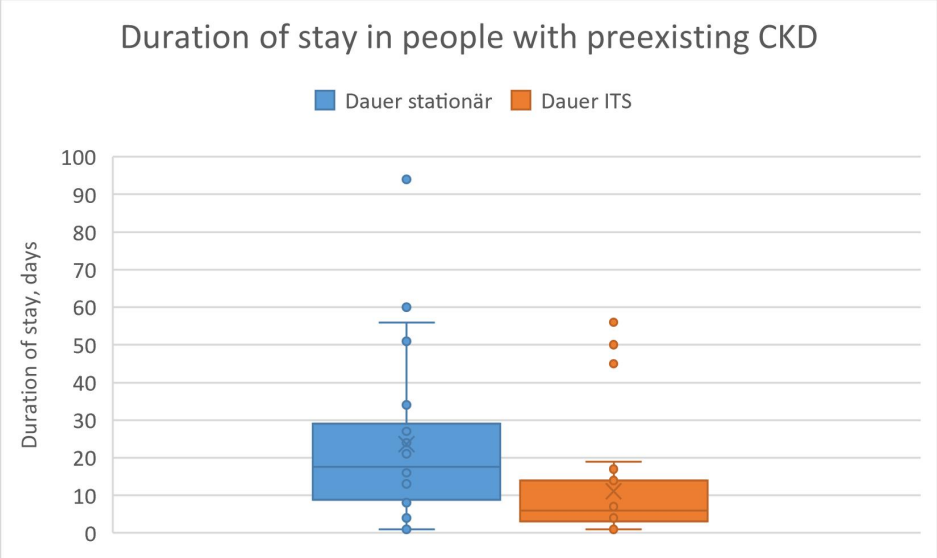

Figure 3.8: Hospital and ICU stay in Patients with preexisting CKD. Dauer stationär: Duration of stay at the hospital. Dauer ITS: Duration of stay in the ICU.

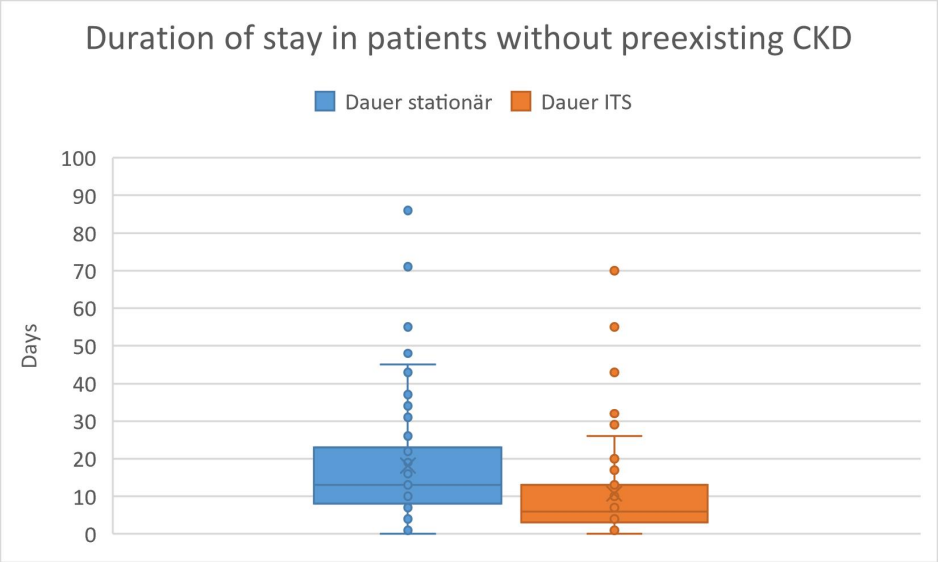

Figure 3.9: Hospital and ICU stay in Patients without preexisting CKD. Dauer stationär: Duration of stay at the hospital. Dauer ITS: Duration of stay in the ICU.

3.2.3 Clinical Presentation

Shortness of Breath

Shortness of Breath was observed in 78 patients. In the patient group without preexisting CKD, 59 patients had shortness of breath, while in the patient group with preexisting CKD, 19 patients had shortness of breath.

Diarrhea

Diarrhea was observed in an overall of 6 patients. In the patient group without preexisting CKD, 4 patients had diarrhea, while 2 patients who had preexisting CKD had diarrhea.

Nausea / Vomiting

Nausea or vomiting was observed in 11 patients. 3 patients who had preexisting CKD had also nausea or vomiting. 8 patients had no preexisting CKD and suffered from nausea or vomiting.

Myalgia

Myalgia was observed in 7 patients. 0 patients had preexisting CKD and myalgia, while 7 patients had myalgia and had no preexisting CKD

3.2.4 Vital Parameters

ICU Admission Temperature

We observed ICU admission Temperature in an overall of 101 patients. 29 patients had preexisting CKD, their median admission temperature was 37.7 (IQR 36.5 - 38.3). 72 patients had no preexisting CKD, their median admission temperature was 37.6 (IQR 37.0 - 38.4).

Blood Pressure

Systolic blood pressure was recorded for 108 out of 111 patients. Out of the 80 patients with no preexisting CKD, 3 were not measured and this patient group had a median systolic blood pressure of 120 mmHg (IQR 98.3 - 149.0). 30 patients with preexisting CKD had a median systolic blood pressure of 120 mmHg (IQR 104.5 - 149.5).

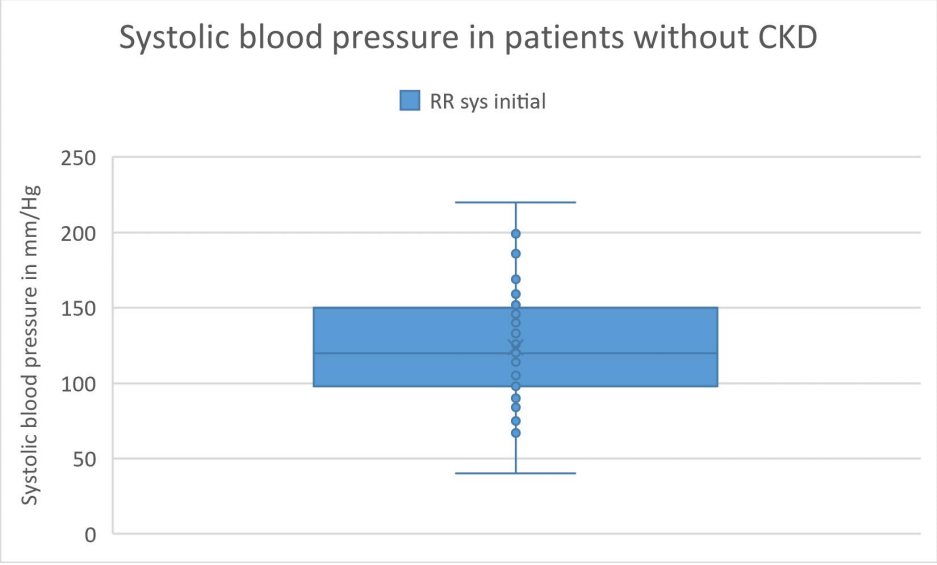

Figure 3.10: Systolic blood pressure of patients without preexisting CKD

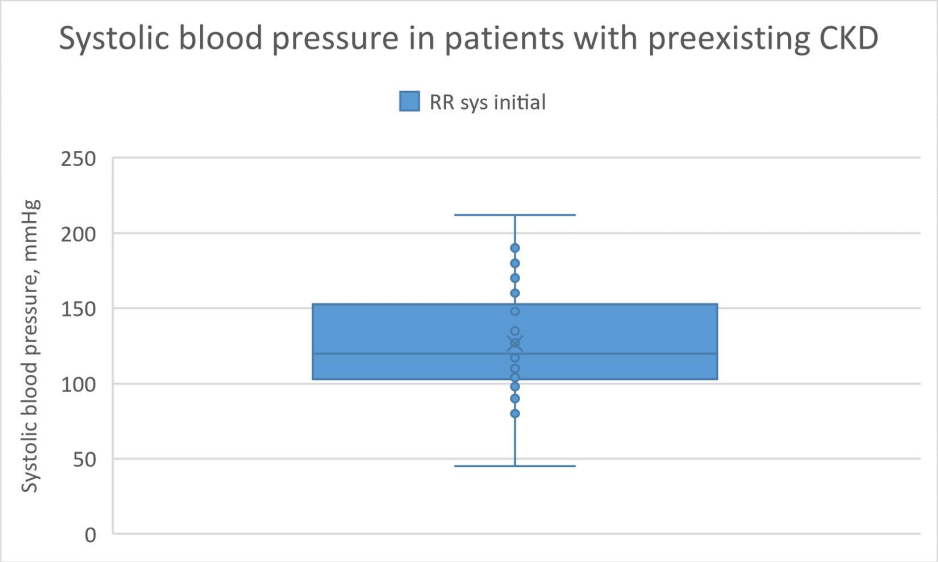

Figure 3.11: Systolic blood pressure of patients with preexisting CKD

3.2.5 Laboratory Values

Leukocytes

We recorded leukocyte levels in every patient. The leukocyte counts fell within a normal range of 4.4 to 11.3 x10^9/L. Counts below 4.4 x10^9/L were classified as leukopenia, while counts above 11.3 x10^9/L were categorized as leukocytosis. The median leukocyte count of all patients was 8.52. (IQR 6.11 - 11.98). Median leukocyte count of the patient group with preexisting CKD was 7.47 (IQR 5.7 - 10.7). Median leukocyte count of the patient group without preexisting CKD was 8.9 (IQR 6.2 - 12.6).

		Total	Patients with preexisting CKD	Patients without preexisting CKD	Significance
Leukocytes		N=111	N= 30	N = 81	0.6687
	Leukopenia	17	4	13	
	Normal	62	19	43	
	Leukocytosis	32	7	25	

Table 3.13: Leukocytes in Patients with and without preexisting CKD

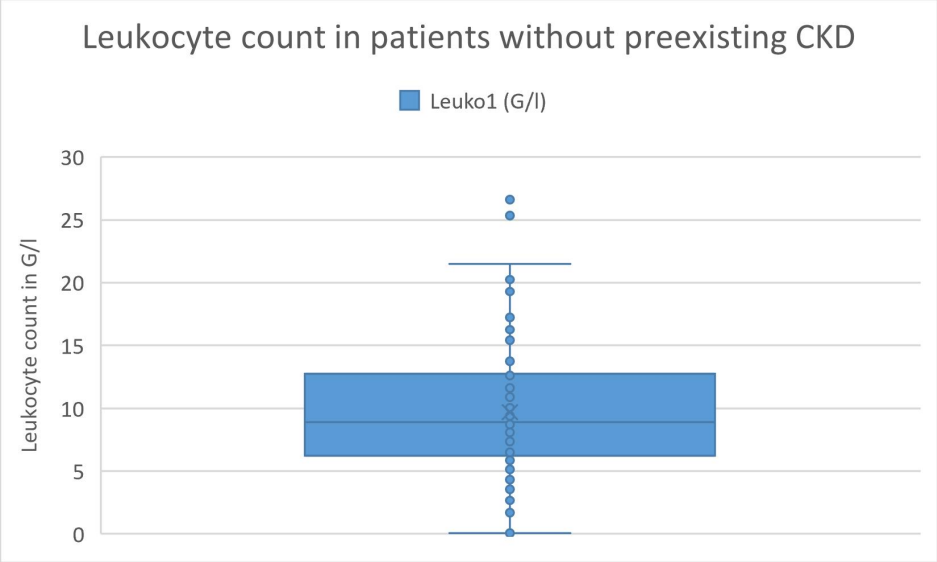

Figure 3.12: Leukocyte count in patients without preexisting CKD

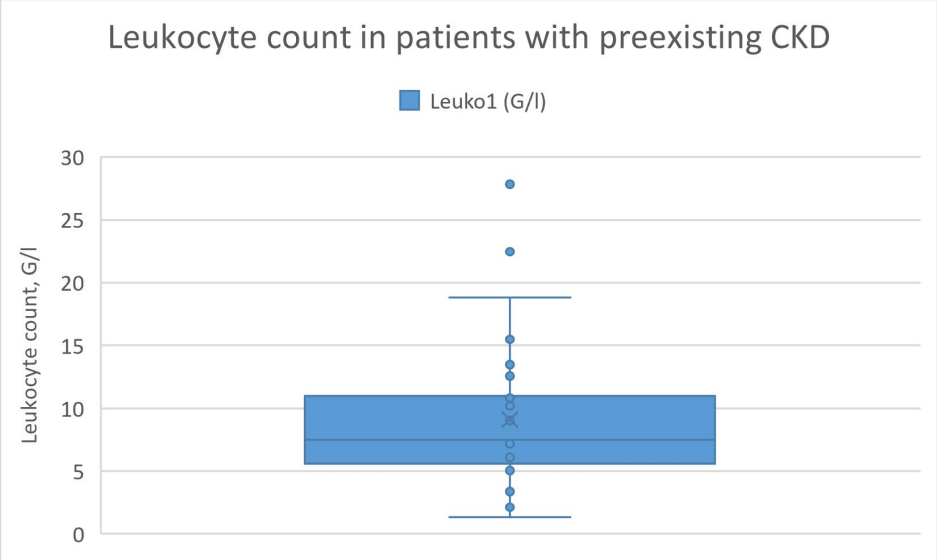

Figure 3.13: Leukocyte count in patients with preexisting CKD

Hemoglobin and Hematocrit

In all patients, hemoglobin and hematocrit levels were assessed. Normal hemoglobin levels for men ranged from 13.0 to 17.5 g/dL, while for women, they ranged from 12.0 to 15.3 g/dL. Hemoglobin levels below 13.0 g/dL in men and below 12.0 g/dL in women indicated anemia. Conversely, hemoglobin levels exceeding 17.5 g/dL in men and 15.3 g/dL in women indicated elevated hemoglobin levels.

Normal hematocrit levels for men ranged from 40 percent to 50 percent, while for women, they ranged from 35 percent to 45 percent. Hematocrit levels below 40 percent in men and below 35 percent in women indicated low hematocrit levels, whereas levels exceeding 50 percent in men and 45 percent in women indicated high hematocrit levels.

In the patient group without preexisting CKD, the median hemoglobin was 13.7 g/dL (IQR 11.5 - 15.1). In the patient group with preexisting CKD, the median hemoglobin was 10.7 g/dL (IQR 9.6 - 11.7)

		Total	Patients with preexisting CKD	Patients without preexisting CKD	Significance
		N=111	N= 30	N = 81	
	Low	54	25	29	
Hemoglobin	Normal	53	4	49	< 0.005**
	High	4	1	3	
		N=111	N= 30	N = 81	
	Low	61	25	36	
Hematocrit	Normal	44	5	39	< 0.005**
	High	6	0	6	

Table 3.14: Hemoglobin and Hematocrit in patients with and without preexisting CKD

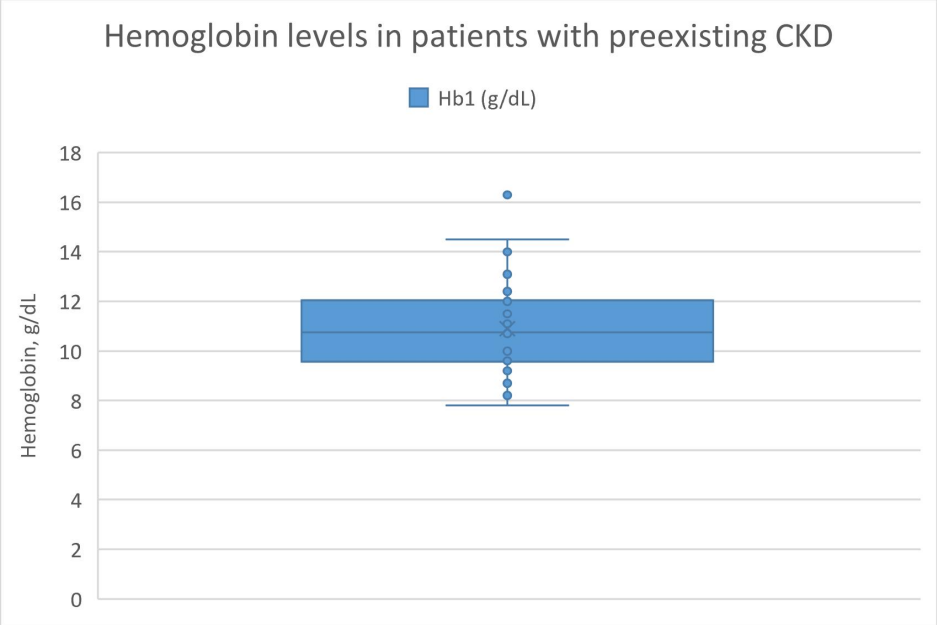

Figure 3.14: Hemoglobin levels in patients with preexisting CKD

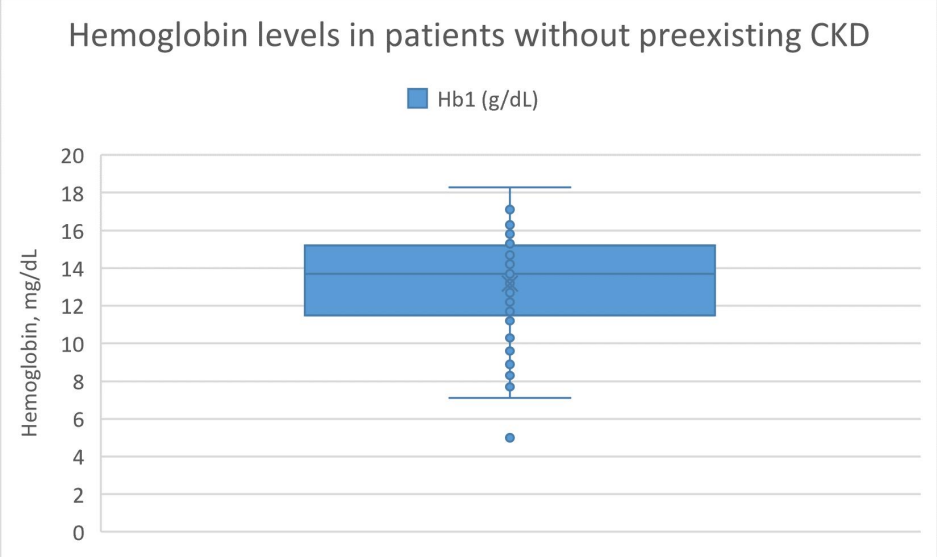

Figure 3.15: Hemoglobin levels in patients without preexisting CKD

Creatinine Levels

In all patients, creatinine levels on hospital admission were assessed. On ICU Admission, 109 patients were assessed. Normal creatinine levels were up to 1.20 mg/dL in men and up to 1.00 mg/dL in women. Creatinine levels exceeding 1.20 mg/dL in men and 1.00 mg/dL in women were considered elevated.

The median creatinine concentration of all patients with preexisting CKD on hospital admission was 1.6 mg/dl (IQR 1.2 - 4.0). The median creatinine concentration on hospital admission in patients without preexisting CKD was 1.03 mg/dl (IQR 0.8 - 1.6).

The median creatinine concentration of all patients with preexisting CKD on ICU admission was 1.94 mg/dl (IQR 1.1 - 3.9). The median creatinine concentration on ICU admission in patients without preexisting CKD was 1.07 mg/dl (IQR 0.8 - 1.5).

		Total	Patients with preexisting CKD	Patients without preexisting CKD	Significance
Creatinine Adm.		N=111	N= 30	N = 81	
	Normal	52	6	46	
	Elevated	59	24	35	< 0.005**
Creatinine ICU		N=109	N= 30	N = 79	
	Normal	54	6	48	
	Elevated	55	24	31	< 0.005**

Table 3.15: Creatinine Counts in patients with and without preexisting CKD

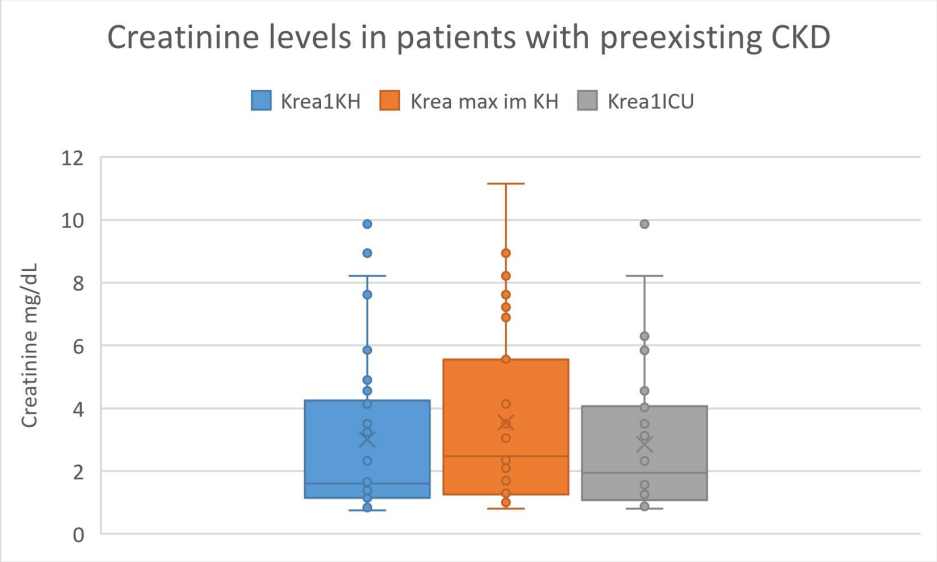

Figure 3.16: Creatinine levels in patients with preexisting CKD

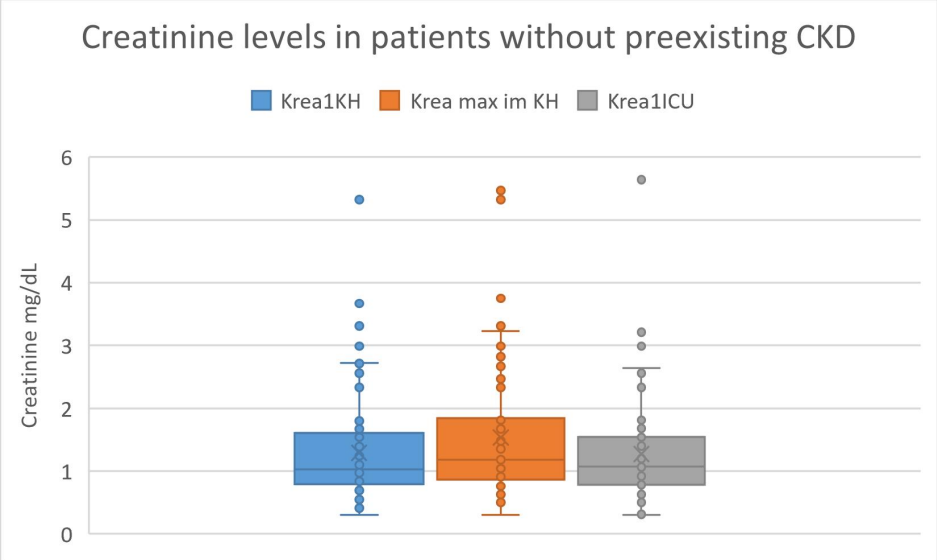

Figure 3.17: Creatinine levels in patients without preexisting CKD

C-Reactive protein

C-Reactive protein levels were measured in all patients. Normal CRP levels were up to 5 mg/L, while levels above 5 mg/L were considered elevated.

In patients with preexisting CKD, the median CRP concentration was 85.4mg/l (IQR 49.4 - 243.8). In patients without preexisting CKD, the median CRP concentration was 93.8 mg/l (IQR 30.7 - 181.4).

		Total	Patients with preexisting CKD	Patients without preexisting CKD	Significance
		N=111	N= 30	N = 81	
CRP	Normal	6	1	5	
	Elevated	105	29	76	1

Table 3.16: C-reactive Protein in patients with and without preexisting CKD

Aspartate transaminase and Alanine transaminase Levels

AST levels were assessed in all patients. Normal AST levels were up to 50 U/L in men and up to 35 U/L in women. AST levels exceeding 50 U/L in men and 35 U/L in women were considered elevated. The normal and elevated levels for ALT were the same as for AST levels.

In patients with preexisting CKD, the median AST concentration was 41 U/l (IQR 26 - 67). In patients without preexisting CKD, the median was 58 U/l (IQR 35 - 110).

In patients with preexisting CKD, the median ALT concentration was 21 U/l (IQR 16 - 37). In patients without preexisting CKD, the median ALT was 31 U/l (IQR 21 - 46).

		Total	Patients with preexisting CKD	Patients without preexisting CKD	Significance
		N=110	N= 29	N = 81	
	Normal	41	14	27	
AST	Elevated	69	15	54	0.1822
		N=110	N= 29	N = 81	
	Normal	81	24	57	
ALT	Elevated	29	5	24	0.2279

Table 3.17: AST and ALT Levels in patients with and without preexisting CKD

Bilirubin

Bilirubin levels within the range of 0.10 - 1.20 mg/dL were considered normal. Levels exceeding 1.20 mg/dL were classified as hyperbilirubinemia.

In patients without preexisting CKD, the median bilirubin concentration was 0.5 mg/dl (IQR 0.3 - 0.9). In patients with preexisting CKD, the median bilirubin concentration was 0.31 mg/dl (IQR 0.2 - 0.9).

		Total	Patients with preexisting CKD	Patients without preexisting CKD	Significance
		N=107	N= 29	N = 78	
	Normal	91	26	65	
Bilirubin	Elevated	16	3	13	0.5490

Table 3.18: Bilirubin in patients with and without preexisting CKD

Lactate dehydrogenase Levels

Normal LDH levels were determined to be between 120 and 240 U/L. LDH levels above 240 U/L were considered elevated. In patients with preexisting CKD, the median LDH concentration was 327 (IQR 239.5 - 434). In patients without preexisting CKD, the median LDH concentration was 313 U/l (IQR 248 - 551).

		Total	Patients with renal complications	Patients without renal Complications	Significance
		N=104	N= 27	N = 77	
	Normal	24	7	17	
LDH	Elevated	80	20	60	0.7913

Table 3.19: Lactate Dehydrogenase Levels in patients with preexisting CKD

N-terminal prohormone of brain natriuretic peptide Levels

Normal NT-proBNP levels were defined as up to 150 pg/mL in women and up to 100 pg/mL in men. Levels exceeding 150 pg/mL in women and 100 pg/mL in men were considered increased NT-proBNP levels. In patients with preexisting CKD, the median NT-proBNP concentration was 6268 pg/ml (IQR 2271 - 16903). In patients without renal complication, the median NT-proBNP concentration was 2488 pg/ml (IQR 444 - 4239.8).

		Total	Patients with preexisting CKD	Patients without preexisting CKD	Significance
		N=43	N= 13	N = 30	
	Normal	3	0	3	
NT-proBNP	Elevated	40	13	27	0.5418

Table 3.20: NT-proBNP Levels in patients with and without preexisting CKD

3.2.6 Blood Gas Analysis

Arterial pO_2, arterial pCO_2, pH and HCO_3 levels were measured for blood gas analysis and the Horovitz index H was calculated:

$$H = \frac{\text{arterial p}O_2}{F_iO_2} \tag{3.2}$$

Normal levels for arterial pO_2 were considered to be between 71 and 104 mmHg. Levels below 71 mmHg were classified as hypoxemic, while levels above 104 mmHg were classified as hyperoxemic. Arterial pO_2 levels were available for 108 out of 111 patients.

Arterial pCO_2 levels within the range of 35-45 mmHg were considered normocapnic. Levels below 35 mmHg were classified as hypocapnic, while levels above 45 mmHg were classified as hypercapnic. It should be noted that arterial pCO_2 levels were not available for 3 patients. [20]

For arterial pH, levels ranging from 7.350 to 7.450 were considered normal. Levels below 7.350 were classified as acidosis, while levels above 7.450 were classified as alkalosis.[20] pH levels were available for 109 out of 111 patients.

HCO_3 levels within the range of 21 to 26 mmol/L were considered normal. Levels below 21 mmol/L were classified as decreased HCO_3 levels, while levels above 26 mmol/L were classified as elevated HCO_3 levels.[20] HCO_3 levels were available for 102 out of 111 patients.

The Horovitz index was calculated by dividing the arterial pO_2 by the fraction of oxygen in the inhaled air (F_iO_2). Normal levels were considered to be above 300. Levels between 200 and 300 were classified as mild ARDS, levels between 100 and 200 as moderate ARDS, and levels below 100 as severe ARDS, according to the Berlin definition. [21]

Median F_iO_2 levels for patients with preexisting CKD were (IQR 0.36 - 0.60). Median F_iO_2 for patients without preexisting CKD was (IQR 0.37 - 0.70).

		Total	Patients with preexisting CKD	Patients without preexisting CKD	Significance
arterial pO_2		N=108	N= 30	N = 78	
	Hypoxemic	39	13	26	
	Normoxemic	38	12	26	0.2280
	Hyperoxemic	31	5	26	
arterial pCO_2		N=108	N= 28	N = 80	
	Hypocapnic	34	8	26	
	Normocapnic	25	6	19	0.8837
	Hypercapnic	49	14	35	
pH		N=109	N= 31	N = 78	
	Acidosis	49	14	35	
	Normal	30	9	21	0.6753
	Alkalosis	30	6	24	
arterial HCO_3		N=102	N= 29	N = 73	
	Decreased	23	7	16	
	Normal	39	11	28	0.9999
	Elevated	40	11	29	
Horowitz Index		N=107	N= 30	N = 77	
	Severe LI	15	5	10	
	Moderate LI	42	11	31	0.9686
	Mild LI	32	9	23	
	No LI	18	5	13	

Table 3.21: Blood Gas Analysis in patients with and without preexisting CKD

3.2.7 Past Medical History - Underlying Disease

Asthma

We observed Asthma in a total of 3 patients. 0 Patients with Asthma had preexisting CKD, while 3 patients had no preexisting CKD.

COPD

We observed COPD in a total of 38 patients. 13 Patients with COPD had preexisting CKD, while 17 patients had no preexisting CKD.

Smoking

We observed a smoking habit in 28 patients. 9 patients had preexisting CKD while 19 had no preexisting CKD.

Coronary heart disease

We observed coronary heart disease in 25 patients. 9 patients had preexisting CKD while 16 had not.

Congestive heart failure

We observed congestive heart failure in 30 patients. 14 patients had preexisting CKD while 16 had no preexisting CKD.

Arrythmia

We observed arrythmia, including all entities and origins, in 32 patients. 13 had preexisting CKD while 19 patients had no preexisting CKD.

Arterial Hypertonus

We observed arterial hypertonus in 60 patients. 22 Patients had preexisting CKD while 38 had no preexisting CKD.

Diabetes Mellitus Type 2

We observed diabetes mellitus type 2 in 18 patients. 6 patients had preexisting CKD while 12 had no preexisting CKD.

Malignancies

We observed malignant tumors in 20 patients. 5 patients had preexisting CKD while 15 had no preexisting CKD.

Immunosuppression

We observed immunosuppression in 15 patients. 6 patients had preexisting CKD while 9 had no preexisting CKD.

Disease	Total N=111	Patients with preexisting CKD N=30	Patients without preexisting CKD N=81	Significance
Asthma	3	0	3	0.5618
COPD	30	13	17	0.2622
Smoker	28	9	19	0.4724
Coronary Heart Disease	25	9	16	0.3073
Heart Failure	30	14	16	0.0076**
Arrythmia	32	13	19	0.0582
Arterial Hypertension	60	22	38	0.0179**
Diabetes Mellitus Type 2	18	6	12	0.5654
Malignancies	20	5	15	1
Immunosuppression	15	6	9	0.2274

Table 3.22: Underlying Disease in patients with preexisting CKD

Mortality and Death

Out of 30 patients with preexisting CKD, 17 survived their illness and 13 patients died during their hospital stay. In the patient group without preexisting CKD, 50 patients survived and 31 succumbed to their illness. This finding was not significant. (p=0.6662)

Chapter 4

Conclusion

4.1 Conclusion

First, we evaluated in this retrospective cohort study the frequency and associated factors of AKI (RIFLE class 2 - 5) in sInfABInf. From 111 patients (median age 66 years), treated at ICUs with sInfABInf, 32 patients (29 percent, median age 71 years) developed relevant renal complications with RIFLE class 2 - 5 (AKI with renal failure). AKI with RIFLE class 2 - 5 the was not significantly associated with lower systolic blood pressure (median 117 mmHg versus 122 mmHg in RIFLE 0 - 1) and had no relevant impact on laboratory values like Hb, leukocyte levels, platelet counts, the median duration of hospital stay (median 14 days versus 14.5 days) or the median duration of ICU stay (median 6.5 days versus 6 days). In contrast, patients with AKI and RIFLE class 2 - 5 had a trend to elevated CRP (median 160 mg/l vs. 80 mg/l in RIFLE 0 - 1), what might be explained by a higher rate of secondary bacterial or fungal infections. A higher risk for severe secondary infections could also be explained be the significant higher rate of immunosuppressed patients in the AKI group with RIFLE 2 - 5 (28 percent versus 8 percent in RIFLE 0 - 1, $p = 0.01$).

Moreover, patients with arrhythmias (47 percent versus 22 percent in RIFLE 0 - 1, $p = 0.01$) were significant more often in the group of AKI and for patients with known preexisting heart failure was at least a clear trend for higher rate of AKI (41 percent versus 22 percent in RIFLE 0 - 1, $p = 0.058$). The mortality rate for patients with AKI (RIFLE class 2 - 5) was finally higher (53 percent versus 34 percent in RIFLE 0 - 1). However, this finding was in our small cohort not statistically significant ($p = 0.087$).

Furthermore, we evaluated the course of sInfABInf in patients with preexisting CKD. From 111 patients, 30 patients (27 percent) had preexisting CKD (median age 71.5 years). There was a trend to older age, however it was not significant. Hospital stay in patients with preexisting CKD was 17.5 days in comparison to patients without preexisting CKD with a median hospital stay of 13 days. ICU stay was the same (6 days) for both groups. There was no significant difference in mortality between the two groups. (43 percent vs 38 percent). Median blood pressure was also the same for patients with preexisting CKD as well as patients without preexisting CKD (120 mmHg).

Preexisting CKD was significantly associated with low hemoglobin as well as low hematocrit ($p = < 0.005$). This finding is most likely due to anemia of CKD.

Preexisting CKD was significantly associated with elevated creatinine at admission to the hospital, as well as admission to ICU ($p = < 0.005$). Median serum creatinine concentration in all patients on hospital admission with preexisting CKD was 1.6 mg/dl. In patients without preexisting CKD it was 1.03 mg/dl. Median creatinine concentration on ICU admission was also significantly higher in patients with preexisting CKD (1.94 mg/dl vs. 1.07 mg/dl).

Considering comorbidity, there was significant association between CKD and heart failure as well as hypertension. Arterial hypertension is a well known risk factor for CKD. Heart failure, on the other side, is also a risk factor in the cohort group of patients with AKI and thus seems to be a constant risk factor.

A preexisting study shows significance regarding a longer hospital stay as well as longer ICU length of stay. We could not replicate this finding in our study, probably due to a smaller cohort group, however there was a clear trend of longer hospital length of stay in our study. [22]

One of our goals in this study was to reevaluate kidney function after two years post ICU or hospital treatment in sInfABInf patients. Sadly, this goal was not attainable, as we lacked sufficient data of renal parameters after treatment for most patients after the hospital stay.

In this study we found a significance both in statistical analysis of acute kidney injury as well as in preexisting CKD, depending on creatine levels. This comes as no surprise, as RIFLE Criteria and CKD is directly dependent on creatinine rise and urinary output. [13, 23]

Also in 3.12 we could show statistical significance for arrythmia, immunosupression as well as pre- and intrahospital RRT.

One patient had no renal complication according to the RIFLE criteria, yet the patient had intra- and prehospital RRT. This could be attributed to either missing documentation in the hospital records or an error during data analysis. Yet this patient does not make a difference in statistical significance.

We could also show in 3.14 that preexisting CKD is statistically associated with lower hemoglobin as well as lower hematocrit. This finding also comes as no surprise, as the kidney is deeply intertwined with fluid balance as well as haematopoiesis. [7, 15]

In 3.22 we could show statistical significance for preexisting CKD in heart failure and arterial hypertension. Hypertension is a well known risk factor for developing CKD. In this study, we found no significance for diabetes mellitus type 2, although this is also a well known risk factor for the development of CKD.[7, 15] This is most likely due to our limited number of patients.

We could also not show statistical significance on the topic of mortality, especially in statistical analysis of patients who met our RIFLE criteria. This is probably due to the aforementioned lacking standardized documentation of urinary output which may would have shifted some patients from the non-RIFLE group into the RIFLE group, as AKI is a well known risk factor in itself when it comes to mortality. [24]

Our study has several limitations. The first limitation is the often insufficient clinical documentation of the parameters listed in the KDIGO criteria. For example, the occurrence of oliguria and/or anuria was often inadequately documented and not standardized, which made it difficult to classify patients in retrospect. The documentation includes statements such as "sufficient diuresis"or "forced diuresis with good excretion". Sometimes the renal function was insufficiently documented, e.g. statements such as "increasing polyuria". This is one of two ways to screen patients for risk of AKI and should be used, as AKI is a serious complication for all patients treated in an ICU.

We thus recommend strict adherence to the guidelines of KDGIO, measuring urinary output in mL/kgKG/h and reevaluating for the first time after 6 hours to include patients who are at risk for AKI and then reevaluating the urinary output all 12 hours. [25]

We recommend further studies into these topics, as they are of high interest to patients and their outcome.

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