How does the presence of Gram-positive and Gram-negative bacteria in various clinical samples relate to levels of inflammation markers?

van den Boom, Nadja Viviane

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GRADUATION THESIS

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Thesis mentor: Assistant Professor, Mirna Bobinac, PhD, M.D.

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1. Full Professor, Alen Protić, Phd, M.D. (President of the Committee)
2. Full Professor, Vlatka Sotošek, PhD, M.D.
3. Assistant Professor, Đurđica Cekinović Grbeša, PhD, M.D

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Abbreviation

AMR	Antimicrobial resistance
CRP	C-reactive protein
DAMPS	Damage-associated molecular patterns
F	Fibrinogen
HAIs	Hospital-acquired infections
ICU	Intensive care unit
ICAM-1	Intercellular adhesion molecule 1
IL-6	Interleukin-6
LPS	Lipopolysaccharide
MRSA	Methicillin-resistant Staphylococcus aureus
MDR	Multidrug resistance
PAMPs	Pathogen-associated molecular patterns
PCT	Procalcitonin
SD	Standard Deviation
VCAM-1	Vascular adhesion molecule 1
WBCs	White blood cells

1. Introduction

Antimicrobial resistance (AMR) represents a significant health challenge worldwide. It is exacerbated by the widespread overuse of antibiotic treatment. The increased antimicrobial resistance can lead to complications, severe infections, prolonged hospital stays and increased mortality rates. Moreover, the overprescription of antibiotics is related to a greater risk of side effects, more frequent re-visits at a doctor's office and increased medical treatment in case of self-limiting diseases (1). This illustrates that AMR is one of the most significant threats to the health of humans worldwide. One of the AMRs is methicillin-resistant Staphylococcus aureus (MRSA), which kills more humans living in America each year than homicide, HIV/AIDS, emphysema and Parkinson's disease combined (2). At the same time, hospital-acquired infections (HAIs) increase annually and resemble a notable health problem requiring urgent attention (3). It has been proven that there is a link between HAI and multidrug resistance (MDR). This impedes the treatment of HAI and again leads to several complications, like increased hospital stay and increased mortality. MDR pathogens represent a crucial cause of hospital infections, especially in the ICU (intensive care unit) (4).

All those aspects emphasise the importance of correct antibiotic treatment to decrease AMR in order to minimise the complications resulting from antibiotic overuse. Now, imagine there would be a parameter leading you in the direction of the type of infection the patients have. A simple parameter, which is taken from the patient's blood in everyday settings. A parameter that could aid in adjusting the antibiotic treatment early, even before the results of the microbiology samples have arrived. It could give the patient extra time instead of waiting for days for the microbiology results and help them recover faster. Sometimes, these few days can be lifesaving for a patient. This importance leads to the idea of this study, which will be explained in the following.

This study will analyse values of fibrinogen, C-reactive protein (CRP), Procalcitonin (PCT), and leukocytes over a period of seven days in ICU settings in patients with different antimicrobial findings (gram-positive infections versus gram-negative infections). The study aims to see if one or several of these parameters can be used as a prognostic factor for detecting the type of infection. First, background knowledge will be provided.

1.1 Bacteria

Bacteria can be classified into gram-positive and gram-negative bacteria based on their structure of cell walls, distinct biological behaviours, and varying host immune responses.

While gram-negative bacteria possess a thin peptidoglycan cell wall surrounded by an outer membrane containing lipopolysaccharides, gram-positive bacteria miss this outer membrane. Instead, they are identified by a thick peptidoglycan layer. The outer membrane is a characteristic component of gram-negative bacteria. It consists of a lipid bilayer with attached glycolipids, mostly lipopolysaccharide (LPS) (5). Two main classes of proteins are found here: Lipoproteins, which are attached to lipids and ß-barrel proteins. They act like porins and facilitate the transfer of molecules (6). LPS are crucial for a functional outer membrane barrier (7). They bind to each other strongly, especially when magnesium cations are present, and overcome the negatively charged phosphate groups from molecules. The saturated acyl chains of LPS create a densely packed barrier impeding the passage of hydrophobic molecules (8). The peptidoglycan cell wall determines the shape of the cell due to its rigidity. It can give bacteria their typical rod shape (9). Certain antibiotics target this barrier and impair the peptidoglycans, eventually leading to cell lysis.

In contrast, the gram-positive cell envelope differs in various key points from its gram-negative complement. As previously mentioned, gram-positive bacteria lack the outer membrane. To compensate for the missing barrier, it provides a very thick layer of peptidoglycans, 30-100 nm thick and composed of many layers. The peptidoglycans are covalently attached to anionic polymers named teichoic acids. Another polymer class is lipoteichoic acid, which is linked to the membrane lipids (10). The cell wall of gram-positive bacteria is composed of 60% of those polymers. Therefore, they contribute mainly to the function and structure of the envelope of the gram-positive bacteria. Additionally, various proteins are anchored to the surface of the gram-positive bacteria. They have different features that aid them in staying close to the membrane. For example, some proteins contain helices to anchor to the membrane (11). These structural diversities influence bacterial pathogenicity and trigger diverse host immune reactions (5).

1.2 Fibrinogen

Fibrinogen is not only involved in homeostasis but also plays a vital role in mechanisms of host defence. It participates in the inflammatory process of bacterial infections and can be used as an important biomarker. The infection triggers an inflammatory response in the host, leading to an increase of acute phase proteins. Fibrinogen belongs to those acute phase proteins (12). It involves two different mechanisms that consider host defence. Firstly, fibrin with soluble fibrinogen encapsulates microbes and limits the dissemination and growth of the

pathogen. This happens predominantly in bacterial infection. Secondly, fibrin participates in the recruitment and activation of immune cells, especially leukocytes. It binds both non-integrin and integrin receptors and thus activates the immune cells. Those receptors are found on macrophages, endothelial cells, neutrophils, and more cells. Through this, fibrinogen can direct a multiplicity of cellular events, like chemotactic, mitogenic and immunoregulatory functions. (13).

1.3 C- reactive Protein

C-reactive Protein (CRP) is an acute phase reactant that can increase up to 1,000-fold in the phase of inflammation or infection. It is primarily synthesised in hepatocytes of the liver but can be synthesised by lymphocytes, adipocytes, endothelial cells, macrophages, and muscle cells. Transcriptional induction starts as a response to high levels of inflammatory cytokines, particularly interleukin-6 (IL-6) (14). Different factors can influence the baseline of CRP, such as age, gender, weight, smoking status, blood pressure, and lipids. CRP plays an essential role in inflammation and host responses to different kinds of infection, including nitric oxide release, phagocytosis, apoptosis, complement pathway and cytokine production (15). In an inflammation process, CRP has the central role of activating C1q in the complement pathway, which leads to the opsonisation of the microbe. Additionally, it binds to Fc receptors of IgG (16). This binding results in the release of inflammatory cytokines (17). Although CRP levels are increased in bacterial infections (18), CRP cannot be used to differentiate between various types of infections. It instead helps to detect an infection rather than differentiate it (19).

1.4 Procalcitonin

Procalcitonin (PCT) is another acute phase reactant (20). Parafollicular cells of the thyroid gland produce PCT under normal conditions. Afterwards, it is converted to calcitonin and released from parafollicular cells. However, in case of inflammation, procalcitonin can be activated in other locations, like kidney, liver, pancreas, adipocytes, brain, and colon. This activation is mediated by inflammatory markers, LPS, and microbial toxins released by inflammation. The non-thyroid-produced PCT is directly released into the bloodstream, unlike procalcitonin, which is produced by the thyroid gland. Procalcitonin can be used as a sensitive marker for observing the progression of infections, particularly for sepsis and pneumonia (21). PCT is a marker for bacterial infection because it does not rise in viral infection and

decreases after adequate antibiotic treatment (22). This makes PCT a unique inflammatory biomarker because other markers like CRP cannot distinguish accurately between non-bacterial and bacterial infections (23). Additionally, PCT rises earlier and decreases to a normal level faster than CRP. This is helpful in early diagnosing a disease and observing disease progression (24).

1.5 Leukocytes

Leukocytes play a significant role in the immune system. They contribute to both the humoral and innate immune system. The classification of leukocytes is according to the presence of granules in the cytoplasm. Granulocytes, meaning the presence of granules, can be further classified into basophils, neutrophils, and eosinophils. Agranulocytes, meaning the absence of granules, are further divided into monocytes and lymphocytes. Each cell type has a specific function in the immune system. The main component of circulating leukocytes is neutrophils, with 50% to 70%. They are responsible for the initial defence line. Their functions include phagocytosis and acute inflammatory reaction to infection with bacteria. Additionally, they are the main cells arriving at the infection site due to diapedesis, which will be explained in the following. After recognising bacteria's foreign antigens, they degrade the bacteria within phagolysosomes with the help of lysosomes (25). Basophils are able to expand rapidly in the bone marrow in case of inflammation and travel via blood to different organs. They resemble mast cells in their function and their phenotypes, and it is difficult to distinguish between them both (26). Eosinophils promote allergic reactions and participate in immune responses against parasites (27). When looking at the agranulocytes, lymphocytes and monocytes can be explained in more detail. Lymphocytes can be further classified into three different subgroups. Their primary role is to produce antibodies and to regulate immune response. Additionally, they are responsible for the direct killing of tumor and virus-infected cells (28). Monocytes contribute to the innate immune system. They are able to differentiate into macrophages and dendritic cells. Monocytes are responsible for regulating cellular homeostasis, particularly in the presence of an infection (29).

A cornerstone of the defence mechanism of the human body is the inflammatory response. It aims to eliminate pathogens such as viruses and bacteria to prevent tissue and organ damage. In acute inflammation, leukocytes get recruited, and the vascular permeability increases within minutes or hours. The leukocyte recruitment can be described as a multistep cascade called diapedesis (30). It is mediated by damage-associated molecular patterns (DAMPs) and

pathogen-associated molecular patterns (PAMPs), which can be found on microbes. These patterns are detected by local inflammatory cells, specifically mast cells and macrophages, and lead to the release of cytokines. It aims the migration of leukocytes out of body circulation (25). Once an inflammation arises, the endothelium is activated, generating several adhesion molecules: E-selectin, ICAM-1 (intercellular adhesion molecule 1), and VCAM-1 (vascular cell adhesion molecule 1). Additionally, chemokines are produced to facilitate the immune response. The selectin ligands alleviate the rolling of leukocytes. Afterwards, the leukocytes arrest due to the adhesion of ß2 integrins to ICAM-1 on the endothelium. In this process, they flatten to reduce the area exposed to the shear stress force of the passing blood. Following this step, the basement membrane crossing of the leukocytes occurs. It preferentially occurs at the site where laminin and collagen density are lower. The leukocytes are able to migrate to the inflammatory area (30).

2. Aims and Objectives

This study aims to analyse if the markers fibrinogen, CRP, procalcitonin, and leukocytes can help distinguish a gram-negative infection from a gram-positive infection. The first goal is to compare the values of the four mentioned markers between the group of patients with a gram-negative infection and those of the group of patients with a gram-positive infection. Secondly, we focus on the correlation between the four markers mentioned above in the group of gram-negative infected patients and the group of gram-positive infected patients. Another goal is to analyse the correlation within each parameter per day to identify any possible differences in both groups. Finally, we test whether fibrinogen can be a useful marker in distinguishing the type of infection.

3. Participants and study design (Materials and methods)

3.1 Study design

In this retrospective study, patients were selected using a convenience sampling method. This method was chosen due to the availability of participants. The patient's medical records were used that were treated at the Department of Anaesthesiology and Intensive Care, Clinical Hospital Center Rijeka, in the period from January 1, 2022, to October 31, 2023. In analysing this data, 51 patients were chosen to be included in this paper.
The following data of the patients were assessed: The inflammatory markers C-reactive protein, procalcitonin, and leukocytes were collected on days one, three, five, and seven. Additionally, fibrinogen values on days one, three, five, and seven were gathered. The type of

infection (gram-positive or gram-negative bacteria) was recorded to understand the relationship between the inflammation markers and the different bacterium types.

3.2 Sample

The convenient patient sample consisted of 39 male and 12 female patients (Table 1). 21 patients revealed a gram-negative infection, 11 showed a gram-positive infection, 10 were sterile, and nine had a fungal infection. Moreover, the patients were classified according to their reason for admission to the ICU: 26 patients had sepsis, and 25 patients were admitted due to trauma.

Table 1: main variables

Characteristics of the samples	**in % (n)**
Full sample	100% (n=51)
Gender *Male* *Female*	 76,47% (n=39) 23,53% (n=12)
Gram-negative infection (G=0)	41,18% (n=21)
Gram-positive infection (G=1)	21,57% (n=11)
Sterile	19,61% (n=10)
Fungal infection	17,65% (n=9)
Sepsis	50,98% (n=26)
Trauma	49,02% (n=25)

3.3 Analysis

In this study, we used descriptive statistics (mean, median, standard deviation), correlations (Pearson correlation, significance level 5% or 10%) and graphical depictions of the data. Additionally, we performed a Student t-test to analyse our results.

4. Results

4.1 Descriptive Statistics

Table 2: Fibrinogen, CRP, Procalcitonin and leukocyte values on day one, three, five and seven in patients with a gram-negative infection and in patients with a gram-positive infection

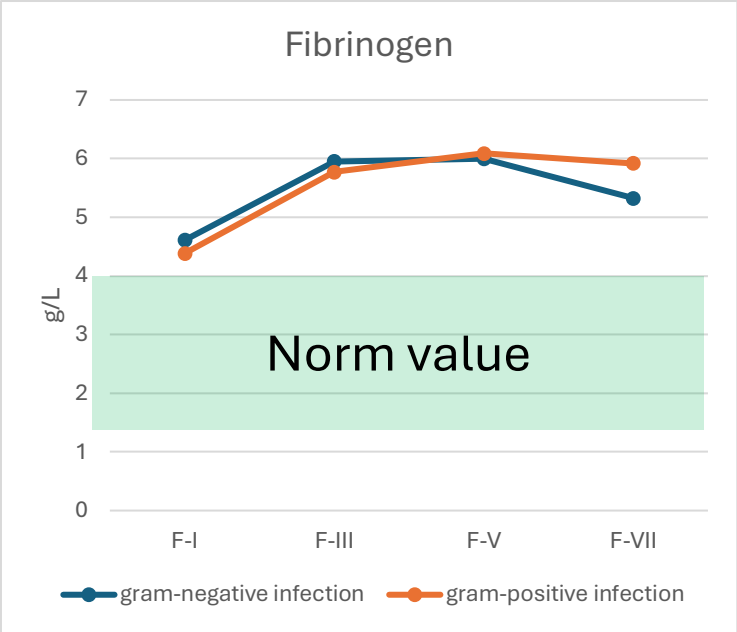
		Gram-negative infection (G=0)			**Gram-positive infection (G=1)**		
		Median	*Mean*	*SD*	*Median*	*Mean*	*SD*
Fibrinogen [g/L]	*F-I*	4,01	4,61	2,58	4,23	4,39	2,28
	F-III	6,33	5,95	1,82	5,28	5,77	1,06
	F-V	6,17	6	1,79	5,85	6,09	1,2
	F-VII	5,88	5,33	1,74	6,36	5,92	1,61

CRP [mg/L]	*C-I*	86,5	136,33	120,22	83,6	140,26	146,78
	C-III	225,4	229,09	97,91	175,6	210,3	120,1
	C-V	183	178,98	76,92	195,9	189,92	91,1
	C-VII	143,6	143,73	94,84	157,1	161,48	72,9
Procalcitonin [ug/L]	*P-I*	1,35	8,45	16,18	1,33	8,08	15,16
	P-III	1,07	7,29	13,54	1,4	4,06	5,25
	P-V	1,06	3,18	4,71	0,69	5,81	12,5
	P-VII	0,46	1,52	2,13	0,48	5,06	10,04
Leukocytes [x109/L]	*L-I*	12,1	11,49	4	7,1	8,27	4,94
	L-III	11,6	12,28	5,71	8,5	8,94	4,14
	L-V	10,5	10,85	4,23	11,4	11,24	3,58
	L-VII	10,1	10,45	3,61	11	10,98	3,34

Table 2 shows the descriptive statistics results. The samples were classified into patients with a gram-negative infection and patients with a gram-positive infection. Table 2 demonstrates the median, mean, and standard deviation (SD) of the four parameters of interest (fibrinogen, CRP, procalcitonin, and leukocytes) on days one, three, five, and seven during the ICU stay. In the following section, each parameter will be described and analysed to see if it correlates with the type of infection.

4.1.1 Fibrinogen

The normal range of fibrinogen (labelled: F) varies between 1,8 and 4,0 g/L (according to the laboratory of Clinical Hospital Center Rijeka range values). On average, F mean values were elevated each day and did not reach the normal value during the ICU stay. Table 2 shows the highest median value was on day seven (F-VII) in the group of gram-positive infected patients (6,36 g/L). The highest mean value of fibrinogen was on day five (F-V) again in the group of patients with a gram-positive infection (6,09 g/L). The lowest fibrinogen mean value was on day one (F-I), also in the gram-positive infected patients group (4,39 g/L). The SD was increased on all measurement days in both groups, with the highest value on F-I in the group of gram-negative infected patients (2,58 g/L). This indicates a relatively large variation around the mean value.

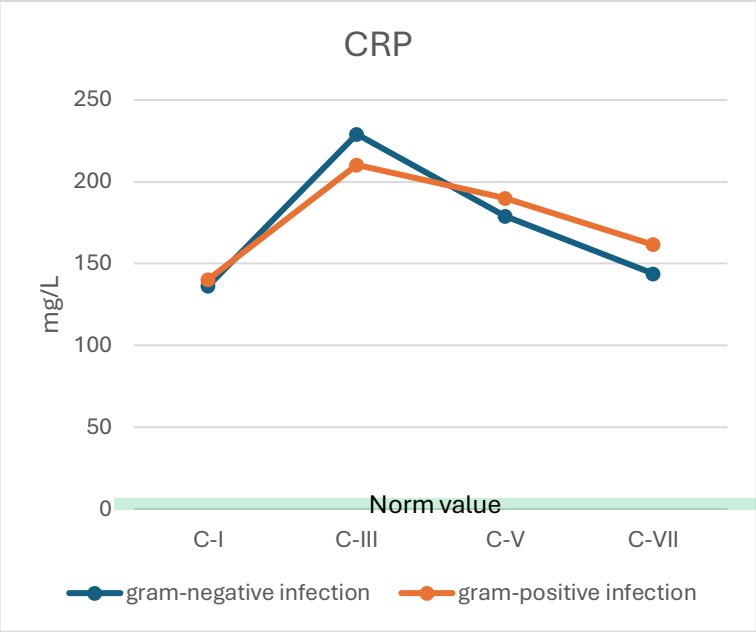


Graph 1: Fibrinogen mean values on days one, three, five, and seven in the group of gram-negative infected patients compared to the group of gram-positive infected patients

Reviewing the trend of the mean values of fibrinogen over seven days revealed no significant differences between both groups (Graph 1): The increase from F-I to F-III in gram-negative infected patients was 29,1%, and in gram-positive infected patients was 31,6%. From F-III to F-V, the mean values of the group with gram-negative patients remained almost the same (increase by 0,8%), while those in gram-positive patients rose by 5,5%. From F-V to F-VII, the fibrinogen mean values decreased more in gram-negative patients (-11,2%) than in gram-positive infected patients (-2,8%).

4.1.2 CRP

The normal range of CRP is below 5µg/L (according to the laboratory of Clinical Hospital Center Rijeka range values). Overall, CRP values were significantly increased on all four measurement days and never reached the normal range in both groups. The highest median CRP value was in the group of gram-negative infected patients on day three (C-III) (225,4 mg/L), while the lowest median CRP value was on day one (C-I) in the group of gram-positive infected patients (83,6 mg/L). Table 2 shows that the lowest CRP mean value was on C-I in the group of gram-negative infected patients (136,33 mg/L), and its highest value was on day three (C-III), again in the group of gram-negative infected patients (229,09 mg/L). The SD was very high in both groups, with the highest value on C-I in the group of gram-positive infected patients (146,78 mg/L). This again indicates the high variance of CRP values in both groups.

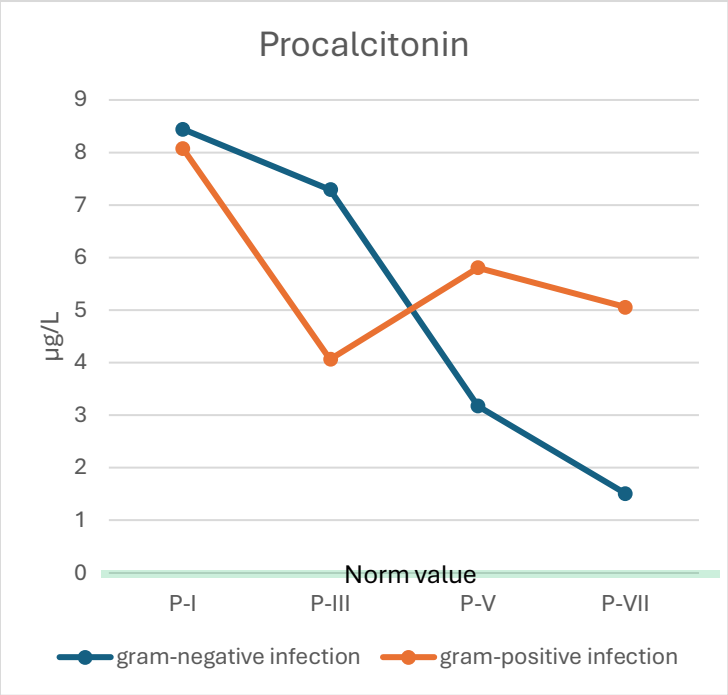


Graph 2: CRP mean values on days one, three, five, and seven in the group of gram-negative infected patients compared to the group of gram-positive infected patients

No remarkable differences were observed in the trend of CRP mean values in both groups over seven days (Graph 2). From C-I to C-III, patients with a gram-negative infection had a higher increase (8,0%) than patients with a gram-positive infection (49,9%). Between C-III and C-V, the CRP mean value decreased in both groups, with a larger drop in patients with a gram-negative infection (-21,9% compared to -9,7%). The CRP mean values decreased between C-V and C-VII in both groups, again more in patients with a gram-negative infection (-19,7% compared to -15%).

4.1.3 Procalcitonin

The following PCT values, as defined by the laboratory of Clinical Hospital Center Rijeka, indicate the following: below 0,046 µg/L indicates a healthy individual, below 0,5 µg/L means a low risk of sepsis, and above 2 µg/L indicates a high risk of sepsis. Overall, PCT values were significantly increased on all four measurement days and never reached the normal range in both groups. Table 2 shows that the highest PCT median value was on day one (P-I) in the group of gram-negative infected patients (1,35 µg/L), while the lowest PCT median value was on day seven (P-VII), again in the group of gram-negative infected patients (0,46 µg/L). The highest mean PCT value was again on P-I in the group of gram-negative infected patients (8,45 µg/L), and the lowest value was also on P-VII in the group of gram-negative infected patients (1,52 µg/L). The SD of PCT values was high every day, with the highest value on P-I in the group of gram-negative infected patients (16,18 µg/L). This indicates again a significant variance around the PCT values.



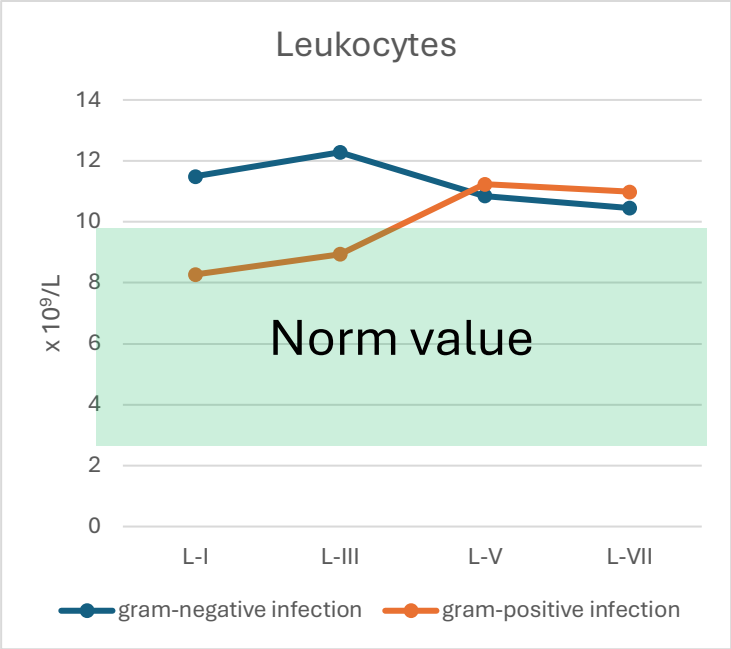
Graph 3: Procalcitonin mean values on days one, three, five, and seven in the group of gram-negative infected patients compared to the group of gram-positive infected patients

When analysing the trend of the PCT mean values in both groups over seven days (Graph 3), some significant differences were observed. On P-I and P-III, the mean PCT values of the gram-negative infection group were higher. However, by P-V and P-VII, the mean PCT values of the group with gram-positive infected patients were higher. In the group of gram-negative infected patients, the PCT mean values constantly fell: Starting slightly from P-I to P-III (-13,7%), then sharply from P-III to P-V (-56,4%) and from P-V to P-VII (52,3%). In contrast, the graph of the patients with a gram-positive infection decreased strongly from P-I to P-III (-49,7%), then increased significantly from P-III to P-V (43,0%) and finally decreased again from P-V to P-VII (-12,9%).

4.1.4 Leukocytes

The normal range of leukocytes varies between 3,4x10^9/L and 9,7x10^9/L (according to the laboratory of Clinical Hospital Center Rijeka range values). On average, leukocyte values were increased on all five measurement days in the gram-negative infected patients, while the values of the first two measurement days (L-I and L-III) were in the normal range in the gram-positive infected patients. Table 2 shows that the highest median value was on L-I in the group of gram-negative infected patients (12,1x10^9/L), while the lowest median value was again on L-I, but in the group of gram-positive infected patients (4x10^9/L). This value is still in the normal range. The highest leukocyte mean value was on day three (L-III) in the group of gram-negative infected patients (12,28x10^9/L), and the lowest mean value was on L-I in the

group of gram-positive infected patients (8,27x10^9/L) being still in the normal range. The SD was increased again on all measurement days, with the highest value on L-III (5,71x109/L), which shows a large variance.



Graph 4: Leukocyte mean values on days one, three, five, and seven in the group of gram-negative infected patients compared to the group of gram-positive infected patients

The trend of the leukocyte mean values in both groups over seven days (Graph 4) differs between both groups. From L-I to L-III, both graphs show an increase, with the group of gram-positive infected patients increasing by 8% and the gram-negative infected patients increasing by 6,9%. Between L-III and L-V, the values of the group of gram-negative infected patients decreased by -11,6%, while the mean values of gram-positive infected patients increased by 25,7%. Between L-V and L-VII, both groups show a decrease (-3,7% and -2,3%).

4.2 Correlation

4.2.1 Correlation between parameters in the group of gram-negative infected patients

Table 3: correlation matrix between fibrinogen and CRP, PCT and leukocytes in the group of gram-negative infected patients (correlation coefficient r and its p-value in brackets)

Gram-negative (G=0)				
	F-I	*F-III*	*F-V*	*F-VII*
C-I	0,82 (0,00)	0,33 (0,15)	-0,05 (0,82)	-0,31 (0,18)
C-III	x	0,37 (0,10)	0,07 (0,77)	-0,26 (0,25)
C-V	x	x	0,22 (0,34)	0,26 (0,26)
C-VII	x	x	x	0,52 (0,02)
P-I	0,16 (0,49)	0,02 (0,93)	-0,30 (0,19)	-0,66 (0,00)

P-III	x	-0,15 (0,50)	-0,36 (0,11)	-0,66 (0,00)
P-V	x	x	-0,57 (0,01)	-0,66 (0,00)
P-VII	x	x	x	-0,21 (0,37)
L-I	-0,18 (0,43)	-0,07 (0,75)	-0,16 (0,49)	-0,04 (0,87)
L-III	x	-0,44 (0,04)	-0,52 (0,02)	-0,48 (0,03)
L-V	x	x	-0,55 (0,01)	-0,57 (0,01)
L-VII	x	x	x	-0,18 (0,43)

Table 3 shows the correlation between fibrinogen, CRP, PCT, and leukocytes in gram-negative infected patients. Overall, the correlation coefficient of fibrinogen with CRP is mainly positive (Table 3). A highly statistically significant correlation exists between F-I and C-I (p=0,00) with a very strong positive linear correlation (r=0,82) (Graph 5). This indicates that high fibrinogen values on day one correspond to high CRP values on the same day. The correlation between F-VII and C-VII indicates a moderate positive linear (r=0,52) relationship, which is significant at the 0,02 level (Table 3). All other combinations show p-values higher than 0,05, indicating no statistically significant correlation.

The correlation coefficients between fibrinogen and PCT are mainly negative (Table 3), indicating that the values are inversely proportional. Three correlations are highly statistically significant: F-VII with P-I, P-III and P-V (r= -0,66 with p=0,00). This leads to the conclusion that F-VII has a strong negative linear correlation with P-I, P-III (Graph 6) and P-V. Another statistically significant relationship exists between F-V and P-V (p=0,01). It shows a moderate negative linear correlation, indicating that the fibrinogen values of day five are inversely proportional to the PCT values on day five.

All correlation coefficients between fibrinogen and leukocytes are negative, indicating a negative linear correlation (Table 3). This means that the leukocyte values tend to decrease while the corresponding fibrinogen values tend to increase. Overall, five correlations are statistically significant. Between F-III and L-III exists a moderate negative linear relationship (Table 3), which is statistically significant (r=-0,44, p=0,04). Another moderate negative linear relationship is the correlation between F-V and L-III (r=-0,52, p=0,02). Three more statistically significant correlations are also in a moderate negative linear relationship: F-V with L-V (r=-0,55, p=0,01), F-VII with L-III (r=-0,48, p=0,03) and F-VII with L-V (r=-0,57, p=0,01).

Table 4: correlation matrix between CRP and PCT in the group of gram-negative infected patients (correlation coefficient r and its p-value in brackets)

Gram-negative (G=0)				
	C-I	*C-III*	*C-V*	*C-VII*
P-I	0,44 (0,05)	0,37 (0,10)	-0,20 (0,39)	-0,45 (0,04)
P-III	x	0,32 (0,16)	-0,19 (0,42)	-0,37 (0,10)
P-V	x	x	0,04 (0,85)	-0,21 (0,36)
P-VII	x	x	x	0,07 (0,76)
L-I	-0,52 (0,02)	-0,03 (0,90)	-0,01 (0,95)	0,01 (0,97)
L-III	x	0,10 (0,68)	0,08 (0,72)	-0,18 (0,43)
L-V	x	x	0,41 (0,06)	0,06 (0,78)
L-VII	x	x	x	0,33 (0,14)

Table 4 represents the relationship of CRP with PCT and leukocytes in patients with a gram-negative infection. Overall, half of the correlations between CRP and PCT are linear positive, and half are negative. However, there are just two statistically significant correlations of CRP with fibrinogen. One is C-I with P-I (r=0,44, p=0,05), indicating a moderate positive linear correlation. The other statistically significant correlation between C-VII and P-I (r=-0,45, p=0,04) shows a moderate negative linear correlation. Hence, this relationship can be described as an inversely proportion.

The correlation between CRP and leukocytes is mainly positive (Table 4). However, there is just one statistically significant correlation, which is a moderate negative linear correlation (C-I with L-I).

Table 5: correlation matrix between PCT and leukocytes in the group of gram-negative infected patients (correlation coefficient r and its p-value in brackets)

Gram-negative (G=0)				
	P-I	*P-III*	*P-V*	*P-VII*
L-I	-0,38 (0.09)	-0,30 (0,19)	-0,14 (0,55)	0,01 (0,96)
L-III	x	0,35 (0,12)	0,52 (0,01)	0,19 (0,40)
L-V	x	x	0,54 (0,01)	0,38 (0,09)
L-VII	x	x	x	-0,24 (0,29)

Table 5 shows the correlation of PCT values with leukocytes in patients with a gram-negative infection. Overall, the correlation coefficients are predominantly positive, with mainly p-values higher than 0,05 (Table 5). Two correlations are statistically significant: P-V with L-II (r=0,52, p=0,01) as well as P-V with L-V (r=0,54, p=0,01) have both moderate positive linear correlations.

4.2.2 Correlation between parameters in the group of gram-positive infected patients

Table 6: correlation matrix between fibrinogen and CRP, PCT and leukocytes in the group of gram-positive infected patients (correlation coefficient r and its p-value in brackets)

Gram-positive (G=1)				
	F-I	*F-III*	*F-V*	*F-VII*
C-I	0,80 (0,00)	0,02 (0,95)	-0,57 (0,07)	-0,52 (0,10)
C-III	x	0,28 (0,40)	0,18 (0,60)	-0,16 (0,63)
C-V	x	x	0,13 (0,70)	0,03 (0,93)
C-VII	x	x	x	0,46 (0,16)
P-I	0,22 (0,53)	-0,14 (0,68)	-0,53 (0,09)	-0,76 (0,01)
P-III	x	-0,09 (0,80)	-0,38 (0,25)	-0,51 (0,11)
P-V	x	x	-0,25 (0,46)	-0,11 (0,74)
P-VII	x	x	x	-0,60 (0,05)
L-I	-0,21 (0,55)	-0,36 (0,28)	0,24 (0,48)	0,32 (0,34)
L-III	x	-0,27 (0,43)	-0,32 (0,34)	-0,44 (0,18)
L-V	x	x	-0,78 (0,00)	-0,77 (0,01)
L-VII	x	x	x	-0,53 (0,10)

Table 6 describes the correlation of fibrinogen values with CRP, PCT, and leukocyte values in gram-positive infected patients. Overall, most of the correlations between fibrinogen and CRP are positive (Table 6). However, just F-I with C-I has a statistically significant correlation (p=0,00). The correlation coefficient (r=0,8) indicates a very strong positive linear correlation (Graph 7), indicating that when fibrinogen on day one is high, the CRP value on day one is high as well. All other correlations are not statistically significant.

The correlation of fibrinogen with PCT is predominantly negative, indicating that most correlations are inversely proportional (Table 6). Two correlations are statistically significant. Firstly, F-VII with P-I is in a strongly negative linear correlation (r=-0,76, p=0,01). As well as F-VII with P-VII (p=0,005) indicating a strong negative linear correlation (r=-0,6).

The relationship between fibrinogen and leukocyte is mostly negative, indicating an inverse proportion (Table 6). The correlation between F-V and L-V, showing strongly negative linearity, is the only statistically significant correlation (p=0,00). This indicates again the trend that while the leukocyte decreases, fibrinogen increases. All other correlations between fibrinogen and leukocytes are not statistically significant (p-value is higher than 0,5).

Table 7: correlation matrix between CRP and PCT and leukocytes in the group of gram-positive infected patients (correlation coefficient r and its p-value in brackets)

Gram-positive (G=1)				
	C-I	*C-III*	*C-V*	*C-VII*
P-I	0,64 (0,04)	0,58 (0,06)	0,32 (0,34)	-0,06 (0,86)
P-III	x	0,61 (0,05)	0,59 (0,05)	0,17 (0,62)
P-V	x	x	0,35 (0,28)	-0,01 (0,98)
P-VII	x	x	x	-0,19 (0,57)
L-I	-0,51 (0,11)	-0,05 (0,89)	0,11 (0,75)	0,51 (0,11)
L-III	x	0,26 (0,44)	-0,12 (0,72)	0,09 (0,80)
L-V	x	x	-0,06 (0,87)	-0,44 (0,18)
L-VII	x	x	x	-0,27 (0,43)

Table 7 shows the correlation between CRP and PCT and leukocytes in the group of gram-positive infected patients. Most correlations between CRP and PCT are positive linear (Table 7). Three pairs are statistically significant. Firstly, C-I correlates with P-I in a strong positive linearity (r=0,64, p=0,04). Another strong positive linear correlation is between C-III and P-III (r=0,6, p=0,05). This means that when the CRP value on day one is increased, the PCT value on day one is increased as well. Similar to the CRP value on day three and the corresponding PCT value on day three. Another statistically significant relation is between C-V and P-III (p=0,05). They show a moderate positive linear correlation (r=0,59), indicating that when the PCT value on day three is high, the CRP level on day five is high as well.

Continuing with the correlation of CRP values with leukocyte values, there is no statistically significant correlation because all p-values are higher than 0,05 (Table 7).

Table 8: correlation matrix between PCT and leukocytes in the group of gram-positive infected patients (correlation coefficient r and its p-value in brackets)

Gram-positive (G=1)				
	P-I	*P-III*	*P-V*	*P-VII*
L-I	-0,47 (0,14)	-0,29 (0,40)	0,06 (0,87)	-0,23 (0,50)
L-III	x	0,20 (0,56)	-0,40 (0,23)	0,01 (0,98)
L-V	x	x	0,40 (0,22)	0,71 (0,01)
L-VII	x	x	x	0,66 (0,03)

Table 8 shows the correlation between PCT and leukocytes in the group of gram-positive infected patients. Most correlations are in a positive linearity (Table 8). Two pairs are statistically significant. Firstly, P-VII with L-V (p=0,01) shows a strong positive linear correlation (r=0,71). Another strong positive linear correlation is between P-VII and L-VII

(r=0,66), which is also statistically significant (p=0,03). This means that when the PCT value on day seven is high, the leukocyte value on day seven is high as well.

4.2.3 Correlation within parameters in the group of gram-negative infected patients

Overall, correlations exist within all four different parameters in the group of gram-negative infected patients. This might be useful in predicting the course of a parameter and considering introducing early treatment or a change of treatment. The following will analyse the correlations within each parameter in the group of patients with a gram-negative infection.

Table 9: Correlation matrix – fibrinogen measurement (correlation within fibrinogen) in the group of gram-negative infected patients (correlation coefficient r and its p-value in brackets)

Gram-negative (G=0)				
	F-I	*F-III*	*F-V*	*F-VII*
F-I	x			
F-III	0,32 (0,16)	x		
F-V	-0,13 (0,57)	0,61 (0,00)	x	
F-VII	-0,28 (0,21)	0,28 (0,21)	0,80 (0,00)	x

Most correlations within fibrinogen are positive. Two pairs are highly statistically significant (Table 9). FIII with FV (p=0,00) is in a strong positive linear correlation (r=0,61). F-V with F-VII is in a very strong positive relationship (r=0,80). This indicates that when a patient has a high fibrinogen value on day three, fibrinogen will also be high on day five. The same is true for when fibrinogen is high on day five; it will also be high on day seven.

Table 10: Correlation matrix – CRP measurement (correlation within CRP) in the group of gram-negative infected patients (correlation coefficient r and its p-value in brackets)

Gram-negative (G=0)				
	C-I	*C-III*	*C-V*	*C-VII*
C-I	x			
C-III	0,39 (0,08)	x		
C-V	-0,13 (0,57)	0,58 (0,01)	x	
C-VII	-0,21 (0,36)	0,32 (0,15)	0,76 (0,00)	x

Similarity can be seen in the correlations within the CRP values. Most correlations are again positive. There are two statistically significant pairs (Table 10). C-III and C-V (p=0,01) are in a moderate positive linear correlation (r= 0,58), while C-V and C-VII (p=0,00) are in a strong positive linear correlation (r=0,76). This implies that high values of CRP on day three will follow high values of CRP on days five and seven.

Table 11: Correlation matrix – PCT measurement (correlation within PCT) in the group of gram-negative infected patients (correlation coefficient r and its p-value in brackets)

Gram-negative (G=0)				
	P-I	*P-III*	*P-V*	*P-VII*
P-I	x			
P-III	0,96 (0,00)	x		
P-V	0,73 (0,00)	0,80 (0,00)	x	
P-VII	0,27 (0,23)	0,32 (0,15)	0,60 (0,00)	x

Most correlations can be found within the PCT values (Table 11). All correlations are positive. There are four statistically significant correlations with two pairs described in a very strong positive linear correlation (P-I with P-III, P-III with P-V) and two pairs in a strong positive linear correlation (P-I with P-V and P-V with P-VII) (Table 11). The correlation graph of P-I with P-III is illustrated by Graph 8. This leads to the conclusion that the PCT values of each day are all in a more or less strong positive correlation.

Table 12: Correlation matrix – leukocyte measurement (correlation within leukocytes) in the group of gram-negative infected patients (correlation coefficient r and its p-value in brackets)

Gram-negative (G=0)				
	L-I	*L-III*	*L-V*	*L-VII*
L-I	x			
L-III	0,27 (0,23)	x		
L-V	0,12 (0,60)	0,76 (0,00)	x	
L-VII	0,07 (0,76)	0,35 (0,13)	0,56 (0,01)	x

All correlations within the leukocytes are positive. Two pairs are statistically significant (Table 12). L-III is with L-V (p=0,00) in a strong positive linear correlation (r=0,76), and L-V is with L-VII (P=0,01) in a moderate positive linear relationship. Hence, the high leukocyte value on day three will follow the high leukocyte value on days five and seven.

4.2.4 Correlation within the parameters in the group of gram-positive infected patients

Table 13: Correlation matrix – fibrinogen measurement (correlation within fibrinogen) in the group of gram-positive infected patients (correlation coefficient r and its p-value in brackets)

Gram-positive (G=1)				
	F-I	*F-III*	*F-V*	*F-VII*
F-I	x			
F-III	0,16 (0,63)	x		
F-V	-0,47 (0,14)	0,59 (0,05)	x	
F-VII	-0,25 (0,46)	0,40 (0,22)	0,84 (0,00)	x

Table 13 shows the correlation within fibrinogen in the group of gram-positive infected patients. Overall, most relationships are positive. The same two pairs, as in the group of gram-negative infected patients, are statistically significant (F-III with F-V and F-V with F-VII) (Table 13). The correlation of F-III with F-V has a moderately strong linearity (r=0,59), while F-V with F-VII has a very strong positive linearity (r=0,84) (Graph 9).

Table 14: Correlation matrix – CRP measurement (correlation within CRP) in the group of gram-positive infected patients (correlation coefficient r and its p-value in brackets)

Gram-positive (G=1)				
	C-I	*C-III*	*C-V*	*C-VII*
C-I	x			
C-III	0,36 (0,28)	x		
C-V	0,27 (0,43)	0,69 (0,02)	x	
C-VII	-0,04 (0,92)	0,46 (0,15)	0,53 (0,09)	x

Again, most of the correlations within CRP are positive (Table 14). One pair is statistically significant. C-III is with C-V (p=0,02) in a strong positive linear correlation (r=0,69). Hence, a high CRP value on day three will follow a high CRP value on day five.

Table 15: Correlation matrix – PCT measurement (correlation within PCT) in the group of gram-positive infected patients (correlation coefficient r and its p-value in brackets)

Gram-positive (G=1)				
	P-I	*P-III*	*P-V*	*P-VII*
P-I	x			
P-III	0,84 (0,00)	x		
P-V	0,13 (0,69)	0,53 (0,09)	x	
P-VII	0,64 (0,03)	0,81 (0,00)	0,82 (0,00)	x

Table 15 shows the correlation within PCT in the group of gram-positive infected patients. All correlations here are positive. Four pairs are statistically significant, while P-I with P-III (r=0,84), P-III with P-VII (r=0,81), and P-V with P-VII (r=0,82) are in a very strong positive linear correlation. P-I and P-VII have a strong positive relationship.

Table 16: Correlation matrix – leukocyte measurement (correlation within leukocytes) in the group of gram-positive infected patients (correlation coefficient r and its p-value in brackets)

Gram-positive (G=1)				
	L-I	*L-III*	*L-V*	*L-VII*
L-I	x			
L-III	0,18 (0,60)	x		
L-V	-0,23 (0,50)	0,18 (0,60)	x	
L-VII	-0,17 (0,61)	0,36 (0,28)	0,56 (0,07)	x

Table 16 shows the correlation within leukocytes in the group of gram-positive infected patients. The correlation is not statistically significant because all p-values are above 0,05.

4.3 Student t-test: Fibrinogen

The t-test is used to determine if there is a statistically significant difference between the fibrinogen means of the two groups. The aim is to see if fibrinogen can be used as a prognostic factor for determining the type of infection, meaning whether it is a gram-positive or gram-negative infection.

Table 17: Student T-test: Fibrinogen values in the group of gram-negative patients (Group 0) and in the group of gram-positive patients (Group 1)

Two-sample t-test with equal variance						
Group	*Obs*	*Mean*	*Std. Err.*	*SD*	*[95% Conf. Interval]*	
0	21	21,88	1,12	5,12	19,55	24,22
1	11	22,17	1,08	3,59	19,75	24,58
combined	32	21,98	0,81	4,59	20,32	23,64
difference		-0,28	1,74		-3,83	3,27

Table 17 shows the student t-test of the sum of fibrinogen values in the group with gram-negative and gram-positive infected patients. Additional information on the t-test results is t=-0,16, degrees of freedom= 30, p-values: one-tailed test (Ha: diff>0): 0,44, two-tailed test (Ha: diff!=0): 0,87, one-tailed test (Ha: diff>0): 0,56.

Comparing the mean values, they are similar (21,88 and 22,17) with just a small difference (-0,28). The t-value is -0,16 with 30 degrees of freedom. This value indicates the standardised difference between the group means. Its small score reveals that the groups are similar. The p-values, which are high with a score over 0,05 (0,87 for the two-tailed test), indicate that the group means are not statistically significant. For the one-tailed tests, the p-values are also higher than 0,05 (0,44, 0,56), demonstrating no significant difference in the specified direction.

5. Discussion

5.1 Discussion of the results

First, all patients in this study received broad-spectrum antibiotics on the first day of their ICU stay. Microbiology samples were taken from each patient on day one to identify potential microbes. After receiving the antimicrobial results, antibiotic treatment was adjusted if necessary.

The descriptive statistics revealed trends in the parameters fibrinogen, CRP, procalcitonin, and leukocytes for both the group of gram-negative infected patients and the group of gram-positive infected patients.

Fibrinogen values were elevated in both groups over the total course of seven days (Graph 1). These elevated values were expected due to their severe illness. Overall, both groups had no significant difference between the mean fibrinogen values. This indicates that fibrinogen responds similarly to the antimicrobial treatment in both groups. Both groups had their lowest fibrinogen mean value on F-I and the highest value on F-V (Table 2). The mean fibrinogen values of the gram-positive group were slightly lower on F-I and F-III (Table 2). Following, on F-V and F-VII, the mean fibrinogen values were higher than the mean values of the patients with a gram-negative infection (Table 2). After F-V, the fibrinogen mean value decreased more in patients with a gram-negative infection (Graph 1), which may indicate that gram-negative patients may return to normal F values faster than gram-positive patients if the trend continues. However, our measurement and our sample size limit any definite conclusion in this respect. The SD, in general, was lower within the patients with gram-positive infection, with the lowest value on F-III (Table 2) indicating a low variance. According to those results, fibrinogen is not a significant marker in distinguishing between gram-positive and gram-negative infections.

CRP values were elevated in both groups over the total course of seven days (Graph 2). This result was again expected due to the patients' severe illness. While the results revealed slight fluctuations in CRP values between both groups, no significant differences could be monitored. This indicates that CRP responds similarly to the antimicrobial treatment in both groups. On C-III, CRP mean values had peaks in both groups (Graph 2). The lowest CRP mean value was for both groups on C-I (Table 2). C-III was the only day where the mean CRP value was higher in the gram-negative infected patients, while on all other days (C-I, C-V, C-VII), the mean CRP value of the group with patients of gram-positive infection was higher

(Graph 2). In patients with a gram-negative infection, the decrease and increase of CRP mean values were greater than those of gram-positive infected patients (Graph 2). The SD was high in both groups, with the highest value on C-III in patients with a gram-negative infection (Table 2). It demonstrates the high variance in median values of CRP. Cause of it can be the small sample size and the fact that in this data, patients with sepsis were not separated from patients with trauma. As a result of this analysis, CRP cannot be used as a significant marker in distinguishing gram-positive from gram-negative infection.

PCT values were significantly elevated on all four measurement days (P-I, P-III, P-V, P-VII) (Graph 3). This was expected due to severe diseases of the patients. Although there were differences in PCT values between both groups, resulting in a dissimilar trend, more research has to be done to conclude a definitive result. The lowest mean PCT value was on P-VII for gram-negative infected patients, while for gram-positive infected patients, the lowest value was on P-III (Graph 3). The highest mean value was for both groups on P-I (Table 2). On P-I and P-III, the PCT mean values of gram-negative patients were higher; on P-V and P-VII, the mean values of the group with gram-positive infected patients were higher (Graph 3). The values of gram-negative infected patients continuously fell, while in the other group, the values increased again on P-V until they fell again until P-VII (Graph 3). Those differences could be explained by the different underlying diseases the patients have. The graph trend of gram-positive infected patients could result from patients suffering from sepsis: The patients are admitted to the hospital with an out-of-hospital infection and have, in the beginning, an increased drop in PCT values. After P-III, the PCT value rises again (Graph 3). In contrast to the graph of gram-negative infected patients, which might resemble patients with trauma. Those patients primarily present with intra-hospital infections, which explains the slower decrease of PCT values in the period. The SD was high again in both groups, with the highest value on P-I in patients with a gram-negative infection (Table 2). In the gram-negative infected patients, the SD decreased daily (Table 2), indicating the variance lowered over the period. The increased values of SD can be again caused due to the small sample size and because patients were not separated into subgroups of sepsis and trauma.

Overall, this is an interesting finding which requires more research in settings of categorising the patients into trauma and sepsis to be able to make a definitive conclusion.

Leukocyte values were partially increased and partially normal (Graph 4). This might happen in bacterial infections. The results of the leukocyte values differ in both groups. The highest mean leukocyte value was on L-III for gram-negative and on L-V for gram-positive patients

(Table 2). Both groups had their lowest leukocyte mean value on L-I (Table 2). When looking at the trends, the mean values of both groups first increased until L-III (Graph 4). The highest mean value was reached for patients with gram-negative infections (L-III). Then, the values of gram-negative infected patients decreased until L-VII (Graph 4). The mean values of gram-positive infected patients initially increased again until they reached their highest mean PCT value on L-V before falling again until L-VII (Graph 4). From L-V, the mean values are similar in both groups, showing no significant difference (Table 2). An important variation is that in the group of patients with gram-positive infections, the mean values of leukocytes on L-I and L-III were still in the normal range (Table 2). This is not the case in the group of patients with a gram-negative infection, as they started directly with increased mean values on L-I and continued over the whole seven days with increased values (Table 2). The SD was similar in both groups and varied slightly between the days, with the highest value on L-II in patients with a gram-negative infection and the lowest value on L-VII in the group with a gram-positive infection (Table 2). However, from L-V, leukocyte values of both groups were very similar, indicating leukocytes do not aid in distinguishing a gram-negative from a gram-positive infection. Overall, the results show that further research, especially in categorising patients into subgroups of trauma and sepsis, is necessary to make a definitive conclusion.

As the next step, the study analysed the correlation between and within each parameter in both groups. We analyse the data by looking at the correlation coefficient (r) and its p-value (p). The null hypothesis states that there is no correlation between the two parameters. We consider a p-value statistically significant when p is higher than 0.05. The correlation of each parameter will be discussed in the following.

There are some similarities in the correlation findings between the two groups. Overall, the correlations among fibrinogen, CRP, PCT and leukocytes were stronger in gram-positive infected patients compared to the group of gram-negative infections. Both groups revealed correlations between all parameters, except in the group of gram-positive infection, where no statistically significant correlation between CRP and leukocytes exists (Table 7). Generally, more negative correlations were found in the gram-negative infections. Therefore, the analysis emphasises that there is no unique correlation specific to either group that could aid in distinguishing between gram-negative and gram-positive infections.

Comparing the correlation results within the different parameters between both groups, some similarities and differences are visible. The most obvious difference is the correlation within leukocytes. In the group of gram-positive infected patients, there is no single correlation

indicating that the leukocyte trend cannot be predicted. In contrast to the group of gram-negative infected patients, there are two significant correlations (Table 12). When comparing the correlation results of CRP in the gram-negative infected patients group, there are two correlations (Table 10); in the other group, there is just one statistically significant correlation (Table 14). C-III with C-V correlation is visible in both groups. The PCT correlation varies in both groups, while both have four statistically significant pairs (Table 11, Table 15). The correlations within fibrinogen show the same two pairs, which are significant in both groups (Table 9, Table 13). This result also emphasises that there is no unique correlation within parameters that could help distinguish between gram-negative and gram-positive infections.

Finally, the t-test showed that there is not enough evidence to reject the null hypothesis. Therefore, there is no significant difference between the means of the two groups. As a result, fibrinogen cannot be used as a prognostic factor for determining the type of infection.

5.2 Limitations of Study

As this study was carried out with a very small sample size, only 51 patients staying in the ICU for a minimum of seven days, it prevents the results from applying to a broader population. Moreover, the data only represents patients from Rijeka hospital, resulting in a one-sided view. This may highlight the working routine of diagnosing and treating patients in Rijeka, which may differ from other hospitals. Another difficulty was identifying suitable patients for the study: Many patients had short stays (less than 7 days) in the ICU, resulting in insufficient data collection days. Additionally, patients with stays of seven days or longer sometimes had missing values of the four investigated parameters. This data could not be included in the study. Another limitation influencing the result of the study is the collection of patients having trauma and sepsis. Clinically, those groups differ, and inflammatory marker values are different. Due to the small sample size, the patients were not subcategorised into sepsis and trauma patients. This leads to a large SD in the results. Another limitation of this study is a sample bias. In this study, the participating patients were not truly selected randomly; it was rather a convenience sampling. Patients were chosen according to their length of stay in the ICU and their underlying disease. So, the results of the study are limited in its generalizability.

5.3 Recommendations for further research

To generalise the study's results to a broader population, increasing the sample size is essential. Including patients from different hospitals would not only enhance the sample size but also avoid the potential bias from a one-sided view. Additionally, subcategorising patients

based on their diseases, such as sepsis or trauma, could aid in reducing SD and obtaining more precise results. Furthermore, monitoring patients after their ICU stay at a normal hospital department (not ICU) to follow the four analysed parameter values until they reach their normal value again could provide valuable insights into the trend of each parameter.

Careful selection of patients is crucial to avoid sample bias. The selection should be truly random to ensure representatives. Extending this data and substantiating or falsifying results in this field is a significant part of future research in this field.

6. Conclusion

When looking at the graphs of the four different parameters (Fibrinogen, CRP, procalcitonin, leukocytes) in both groups, no findings were strong enough to declare them as a prognostic marker for determining the type of infection. Fibrinogen and CRP values were very similar in both groups over the period of seven days (Table 2), indicating they do not help distinguish gram-negative from gram-positive infections. The different graphs of procalcitonin (Graph 3) were interesting and could be explained by the different underlying diseases of the patients, meaning sepsis or trauma. This should be taken as an initial point to start further research and analyse the reason for the difference. Continuing with the leukocyte graphs (Graph 4), it is also not helpful as a prognostic marker for determining the type of infection. They seemed to take different courses in the first three days, but they showed the same trend from day five. Again, more research could be done with a bigger sample size and subcategorisation of underlying diseases to make definite conclusions.

Continuing with the correlation between the four parameters in the two groups, there are strong correlations in the gram-positive infected patients compared to gram-negative infected patients. In both groups, there is a correlation between each parameter except in the group of gram-positive infected patients, where there is no single correlation between CRP and leukocytes (Table 7). Overall, there are more negative correlations in the gram-negative infected patients group than in the other group. Generally, the analysis of the correlation between the four parameters compared between the two groups shows that there is no specific correlation unique for one group and, therefore, could aid in determining the kind of infection. The correlations revealed from this study are not strong enough to conclude the existence of a gram-positive or negative infection.

The same applies to the correlation within the four different parameters. In each group, there are correlations within the before-mentioned parameters, with the difference that the group of

gram-positive infected patients shows not a single correlation within leukocytes (Table 16). These results are not enough to conclude from the within correlations of the parameters which type of infection the patient could possibly have.

Lastly, considering the student t-test, which shows no significant difference between the fibrinogen values, fibrinogen can not be taken as a prognostic parameter for determining the type of infection.

When summarising all the study's findings, there is still room for further research in this field. This was to be expected given the fact that our sample size was very small and that we did not subcategorise the patients according to their underlying disease (sepsis or trauma). This could be a considerable aspect when doing more research in this area.

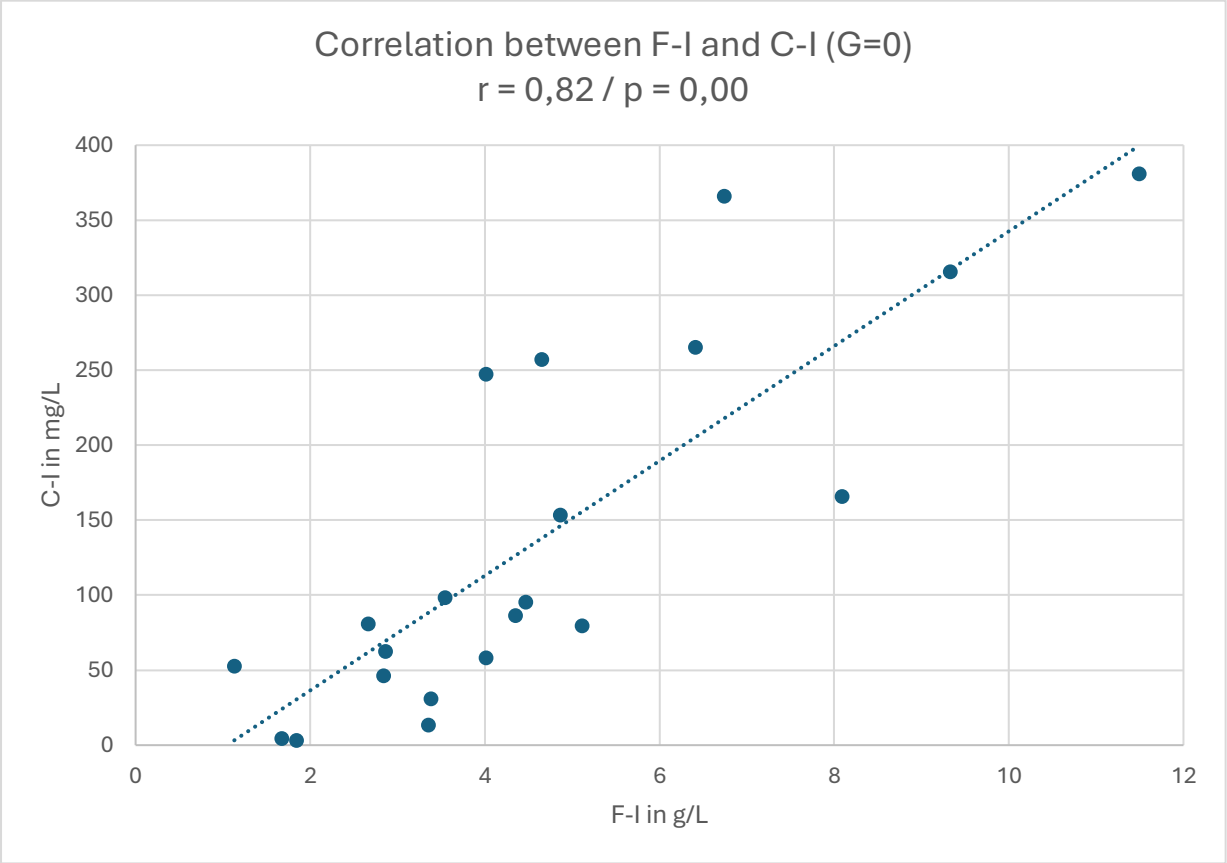
7. Summary

This study reveals that all four parameters of interest (fibrinogen, CRP, procalcitonin and leukocytes) cannot be used solely for distinguishing between a gram-negative and gram-positive infection. Analysing the data revealed some differences between both groups. However, they were not significant enough to conclude that one or more parameters could help determine the type of infection. The study shows limitations, especially a small sample size and no subcategorisation according to trauma and sepsis, which had a significant impact on the study result. Nevertheless, the increasing antimicrobial resistance and intrahospital infections worldwide emphasise the need for appropriate antimicrobial treatment. This shows the importance of further research in this field to improve patient outcomes by choosing appropriate antimicrobial therapy as early as possible.

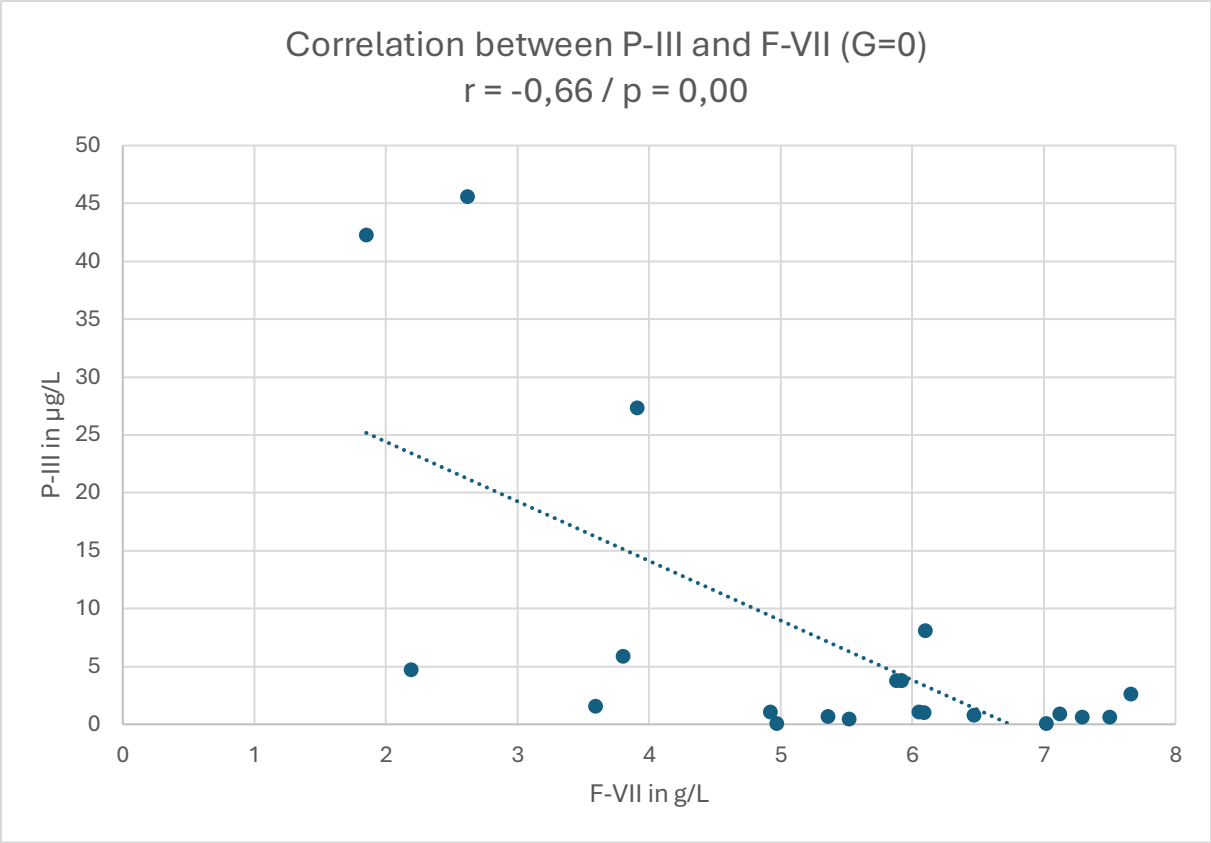
Keywords: bacterial infection, C-reactive protein, Fibrinogen, Procalcitonin, Leukocytes

8. Appendix

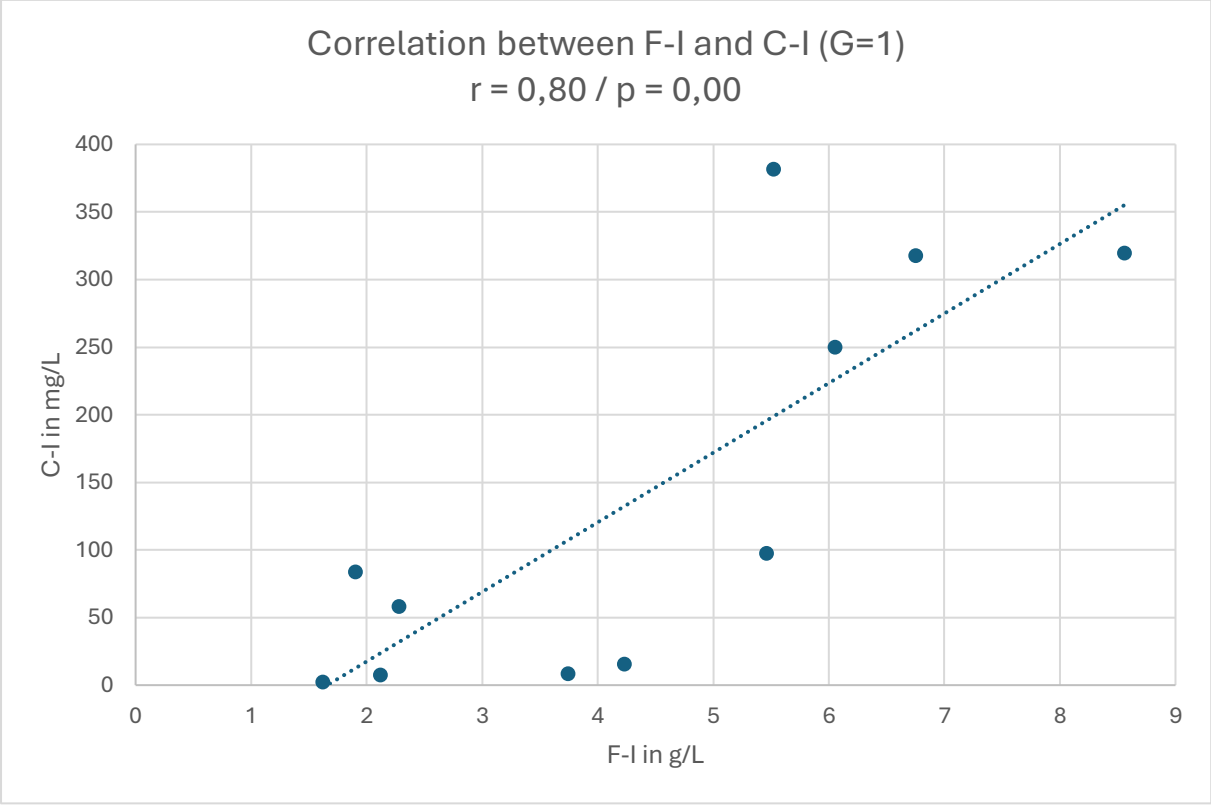
This chapter lists graphs showing the correlations between and within the four parameters of interest. The relations are discussed in more detail in chapter 4.2.



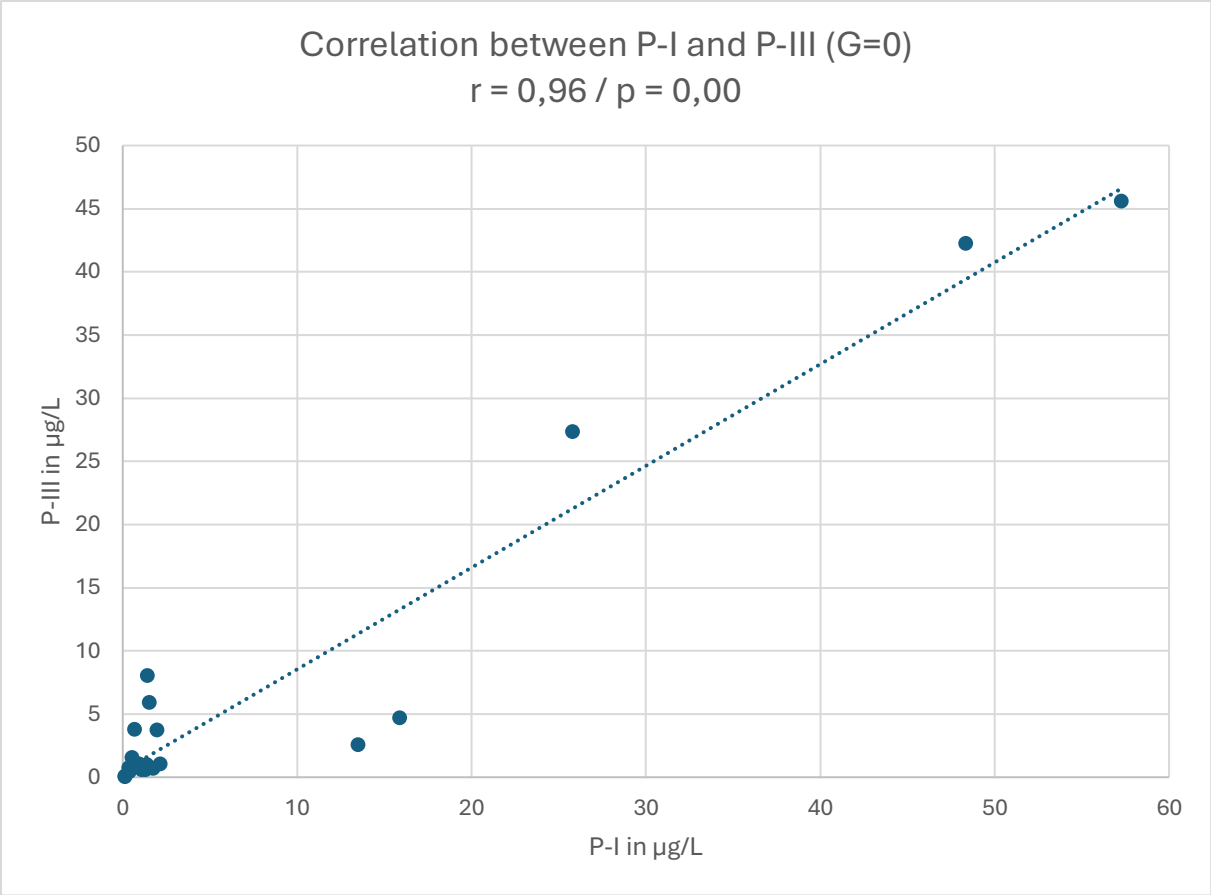
Graph 5: Correlation between F-I and C-I in the group of gram-negative infected patients



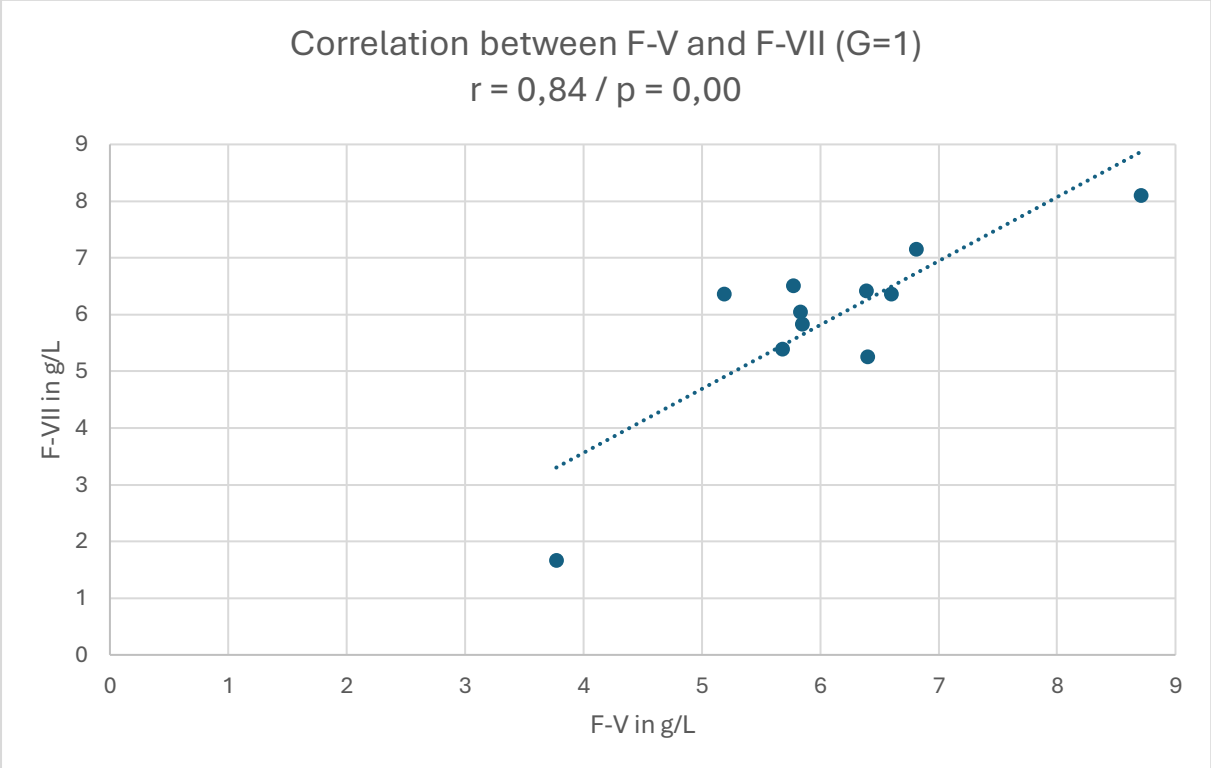
Graph 6: Correlation between P-III and F-VII in the group of gram-negative infected patients



Graph 7: Correlation between F-I and C-I in the group of gram-positive infected patients



Graph 8: Correlation between P-I and P-III in the group of gram-negative infected patients



Graph 9: Correlation between F-V and V-VII in the group of gram-positive infected patients

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9. Curriculum Vitae

Nadja Viviane van den Boom was born on August 5th, 1994, in Leverkusen, Germany. She received her high school diploma from Städtisches Gymnasium Leichlingen in 2013. After graduating, she interned at FANLYC, an aid organisation for children with cancer, in Panama City, Panama. Subsequently, she successfully completed training as a paramedic at Medakademie in Cologne, Germany. Until 2018, she worked as a paramedic for the Langenfeld fire brigade. Since October 2018, Nadja has been studying at the Medical Faculty of the University Rijeka in the English program, where she will graduate in 2024. During her medical studies, she worked as a medical student at a family doctor in Leichlingen (2019) and as a paramedic at Langenfeld Brigade, Germany (2020-2023). Additionally, she attended an internship at the Department of Internal Medicine at Heinrich-Braun-Klinikum in Zwickau, Germany and at a mobile palliative care institution (PalliLev) in Leverkusen, Germany.