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Doctoral Thesis Adstract
Assessment of Inflammatory Biomarkers in complicated Urinary Tract Infection and early diagnosis of Urosepsis

Doctoral candidate,

Guliciuc Mădăllin

Scientific advisor,

Prof Dr Habil Firescu Dorel

Seria M: Medicina   Nr19

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Table of Content

Study I: The role of biomarkers and scores in the description of Urosepsis

1. Introduction

Within the framework of daily urological practice, UTI (Urinary Tract Infection), that becomes complicated with obstructions and progresses to urosepsis, is becoming an increasingly common pathology, having a significant impact on the morbidity and mortality of patients and requiring an increasing allocation of human and material resources for its management. Patients diagnosed with Urinary Tract Obstruction and systemic inflammatory response are at increased risk of developing urosepsis, the consequences of which include increased morbidity, mortality, and associated costs.

Urosepsis is defined as a life-threatening organ dysfunction resulting from an abnormal host response to infections originating in the urinary tract or male genitalia [1]. Septic shock is a subgroup of sepsis characterized by disorders of cellular metabolism and circulatory disorders, associated with a significant increase in the mortality rate. Thus, a broader approach has been taken to distinguish septic shock from cardiovascular dysfunction associated with sepsis and to recognize the importance of cellular metabolic changes [2]. MODS (Multiple Organ Disfunction Syndrome) is characterized by the insufficiency of at least two organs, requiring clinician intervention to maintain homeostasis [3].

Urosepsis accounts for between 9% and 31% of all sepsis cases [4]. It is a serious condition, with an overall mortality rate that can vary between 7.5% and 30% [60]. In addition, the increased morbidity and increased costs associated with the management of this condition underline the importance of prompt and rigorous assessment to ensure rapid access to treatment [5]. Early diagnosis and appropriate treatment can help reduce hospitalization costs, morbidity, and mortality [6].

The diagnosis of urosepsis takes time and can only be confirmed by blood culture during bacteremia and by urine culture [7]. The process of diagnosing these infections can take between 24 and 72 hours, depending on the time it takes to obtain the results of the cultures. In addition, there is a risk of false positive results due to contamination and false negative results due to taking antibiotics before admission to hospital. Therefore, it is necessary to use quick and effective diagnostic methods to distinguish urosepsis from complicated UTI.

Starting from these premises, we analyzed the data already accessible to the clinician that can generate a prompt and specific assessment of the patients' condition, allowing the diagnosis to be established at an early stage and thus ensuring access to appropriate treatment in an

appropriate time limit. For a more accurate assessment of patients, we used PCT [8,9] and validated scores from previous studies, such as qSOFA, SOFA [10], and CCI [11].

The aim of this study is to assess the ability of already existing scores to diagnose, describe the clinical status and predict the progression of patients with cUTI and their risk of progressing to urosepsis.

2. Material and method

To perform this study, we conducted a prospective assessment of patients diagnosed with cUTI who were hospitalized in the Urology Department of the "Sfântul Apostol Andrei" County Clinical Hospital in Galati (GCH), a medical unit with 1220 beds. The data collection period ranged between September 2019 and May 2022. The GCH Hospital is located in the city of Galati, hosting about 250,000 inhabitants. As an important medical institution, GCH provides medical services to the population of the entire Galati County, which has a population of approximately 450,000 people.

Prior to the start of this study, the protocol and procedures were reviewed and approved by the ethics committee of GCH, Galati, Romania, with registration number 24363/2021.

2.1. Patient selection

The inclusion criteria in this study were as follows: patients with cUTIs proven by urine culture or clinically diagnosed, accompanied by SRIS.

The exclusion criteria refer to patients under 18 years of age, pregnant women, people with a history of kidney transplant, patients on hemodialysis or peritoneal dialysis and patients with missing data, necessary for analysis.

2.2. Data collection

Before admission, a thorough clinical examination was performed for each patient. Clinical data were collected, including heart rate, blood pressure, respiratory rate, blood oxygen (PaO$_2$) level, temperature, and Glasgow coma score.

At the time of admission, blood and urine samples were taken, in compliance with International Safety Standards [12]. The values of the blood count, total bilirubin, creatinine and PCT level were analyzed.

For determining the PCT level, the VIDAS BRAHMS PCT automatic analyzer was used, according to the instructions provided by the manufacturer. The lower detection limit of the test was 0.05 ng/mL and the functional sensitivity of the test was 0.09 ng/mL.

All demographic data, clinical and paraclinical findings, as well as diagnostic results were recorded. All patients' medical records were reviewed, and relevant clinical and biological data

were collected. All this information was systematized and analyzed using qSOFA, SOFA and CCI scores.

2.3. Defining variables

PCT is a marker of systemic inflammation and therefore, it can help predict bacteremia [8,9].

For a simpler, faster, and resource-free initial assessment of patients exposed to the risk of sepsis, we used the qSOFA score, which includes assessment of cognitive dysfunction (Glasgow Coma Scale <15), systolic blood pressure (SBP) of 100 mm Hg or lower, and respiratory rate of 22/min or higher [10].

To systematically and objectively describe the clinical status of patients at admission, we used the SOFA score, which assesses the respiratory system, nervous and circulatory system, liver and kidney functions, and coagulation [13]. The usefulness of this score has previously been validated on large groups of patients.

To describe the health status of patients prior to this acute event, we used CCI, which assesses pre-existing mobilities [11].

To assess the impact of this pathology on the health system, the days of hospitalization and the costs related to hospitalization (expressed in Lei, Romanian currency, 1 Leu representing approximately 0.2 Euro) and the days of care in the Anesthesia and Intensive Care Unit (A&ICU) were considered.

2.4. Grouping of patients according to the stage of the disease

Depending on the diagnosis at admission, we divided the patients into three groups: SRIS, sepsis and septic shock. The fourth group is represented by patients who died during hospitalization.

Patients in the "SIRS" group were patients with cUTIs who met the SIRS criteria but did not have sepsis at admission according to the new definition of sepsis. The "sepsis" group includes patients diagnosed with sepsis who did not have organ dysfunction. The patients with septic shock experienced hypotension, despite adequate hydro-electrolyte rebalancing, or SDMO.

2.5. Statistical analysis

Continuous variables were expressed by descriptive statistics, such as mean ± standard deviation (SD) or median and interquartile range [IQR (Q1-Q3)], while categorical variables were summarized by absolute and relative frequencies. All continuous variables were checked for normality, using the Kolmogorov-Smirnov test.

The descriptive statistics were analyzed according to the classification of patients in the previously defined groups (SRIS, sepsis, septic shock, and deceased patients). Variables with Gaussian distribution (e.g., age) were interpreted by means and SD, and the Student's t-test was applied. Variables without Gaussian distribution, such as leukocytes, PCT, SOFA score, qSOFA score, intensive care days, hospitalization days, and hospitalization costs, were analyzed by median and interquartile range [IQR (Q1-Q3)], and the Mann-Whitney test was applied.

The correlation between quantitative variables was assessed using the Spearman Rho correlation coefficient, when appropriate.

An analysis of the ROC curve was performed to assess the discriminant accuracy and to find the threshold values for the variables studied. The threshold level for each variable, depending on the group analyzed, represents the level for which the best values for sensitivity (ability to correctly identify the positive diagnosis) and specificity (ability to correctly identify the negative diagnosis) are simultaneously identified. For all bidirectional statistical tests, significance was considered achieved if the p-value $\leq$ 0.05. The statistical analysis was performed using the MedCalc software, version 12.5.0.0.

3. Results

A total of 174 patients diagnosed with cUTI were included in this study. The statistical values showed an average age of these patients of 61.4 years, with a SD of 15.9 years. Of the total, 107 individuals, representing 61.5%, were male. 116 patients, which corresponds to 66.7% of the total group, came from urban areas.
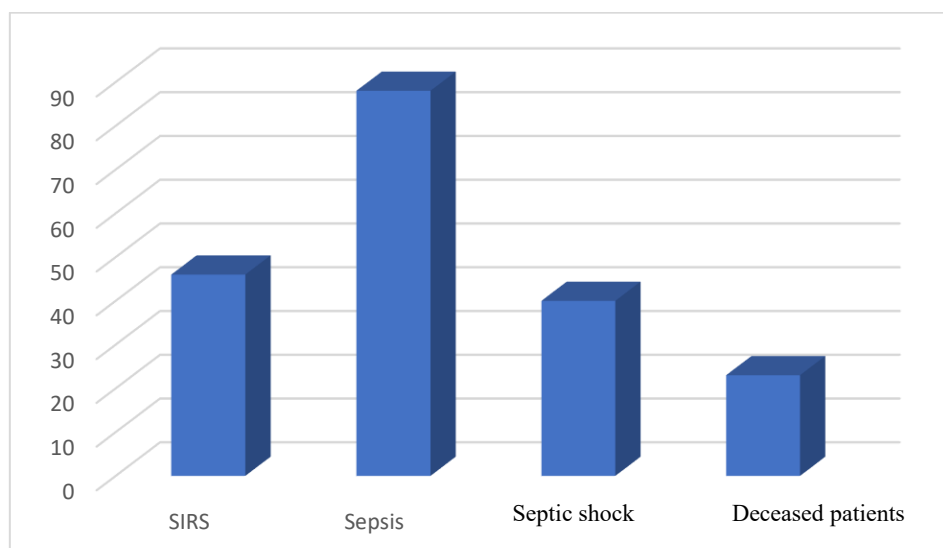
Figure 1. Distribution of patients by groups

Depending on the clinical status of the patients, 46 (24.4%) were classified in the "SRIS" group, 88 (50.6%) in the "sepsis" group, and 40 (22.9%) in the "septic shock" group.

5

A total of 23 (13.2%) of these patients died during hospitalization, thus being enrolled in the "deceased patients" group (Figure 1).

Table 1. Bivariate data analysis according to the groups studied.

	Deceased patients		SRIS		Sepsis		Septic Shock	
	Yes	No	Yes	No	Yes	No	Yes	No
Number	23	151	46	128	88	86	40	134
Age (years) Mean ± SD	71.04 ± 11.03	59.91 ± 16.04	56.84 ± 17.22	62.97 ± 15.17	60.37 ± 15.54	62.40 ± 16.29	69.03 ± 12.72	59.10 ± 16.08
p-value **	<0.001		<0.01		0.40		<0.0001	
Procalcitonin (ng/mL)	32.0 (10.38– 32.0)	7.55 (2.70– 12.2)	2.45 (0.70– 3.20)	11.20 (7.25– 22.32)	9.6 (6.3– 12.2)	4.7 (1.7– 22.1)	24.7 (13.5– 32.0)	6.3 (2.70–10.6)
p-value *	<0.0001		<0.0001		<0.01		<0.0001	
SOFA	10.0 (8.25– 12.0)	5.0 (3.0– 7.0)	3.0 (2.0– 4.0)	7.0 (5.0–9.0)	6.0 (4.0– 7.0)	5.0 (3.0– 9.0)	9.5 (8.0– 12.0)	4.5 (3.0–6.0)
p-value *	<0.0001		<0.0001		0.78		<0.0001	
qSOFA	3.0 (2.0– 3.0)	1.0 (0.0– 2.0)	0.0 (0.0– 0.0)	1.0 (1.0–2.0)	1.0 (0.0– 1.75)	1.0 (0.0– 2.0)	2.0 (2.0– 3.0)	0.0 (0.0–1.0)
p-value *	<0.0001		<0.0001		0.32		<0.0001	
CCI	11.0 (9.2– 13.0)	6.0 (2.0– 8.0)	4.0 (1.0– 8.0)	8.0 (4.0–9.5)	7.0 (3.0– 9.0)	7.0 (3/25– 9/0)	9.0 (7.0– 12.0)	6.0 (2.0–8.0)
p-value *	<0.0001		<0.0001		0.46		<0.0001	
A&ICU days	5.0 (2.0– 8.75)	0.0 (0.0– 1.0)	0.0 (0.0– 0.0)	1.0 (0.0–3.0)	0.0 (0.0– 1.0)	1.0 (0.0– 3.0)	3.5 (2.0– 7.0)	0.0 (0.0–1.0)
p-value *	<0.0001		<0.0001		<0.001		<0.0001	
Days of hospitalization	10.0 (6.25– 18.7)	8.0 (5.0– 13.0)	5.0 (3.0– 8.0)	10.0 (6.5– 17.0)	9.0 (6.0– 13.7)	7.0 (4.0– 13.7)	15.0 (8.0– 22.5)	8.0 (5.0–11.0)
p-value *	0.22		<0.0001		0.12		<0.0001	
Hospitalization cost (Lei)	10855.0 (6752.5 – 24,053. 2)	5329.0 (2230.2 – 9690.5)	2863.0 (1247.0 – 6833.0)	7309.0 (3416.5– 14,994.0)	5836.0 (2351.7 – 9398.2)	6833.0 (2663.7 – 11,805. 0)	14704.5 (7357.0 – 26,103.5)	4437.5 (1914.0– 7967.0)

	Deceased patients		SRIS		Sepsis		Septic Shock	
	Yes	No	Yes	No	Yes	No	Yes	No
*p-value**	*<0.001*		*<0.0001*		*0.40*		*<0.0001*	

*Mann–Whitney U Test; **Student's t-test; SIRS = Systemic Inflammatory Response Syndrome; SOFA = Sequential (Sepsis-Related) Organ Failure Assessment; qSOFA = quick SOFA; CCI = Charlson Comorbidity Index

A detailed analysis of the data in the table showed an upward trend in the age of patients as the severity of symptoms increases. Thus, the mean age was 56.86 ± 17.22 (mean $\pm$ SD) years for patients in the "SIRS" group, 60.37 ± 15.54 years for those in the "sepsis" group, 69.03 ± 12.72 years for those in the "septic shock" group, and 71.04 ± 11.03 years for those in the "deceased patients" group. To assess the relevance of this relationship, we applied the Student's t-Test and obtained statistically significant results, except for the group of patients diagnosed with sepsis ($p = 0.40$) (Table 1).

Considering that age is an essential variable in the calculation of the CCI and given the well-known association between aging and the increased tendency to develop comorbidities, we resorted to the Spearman rank-order correlation analysis to examine the presence of a statistically significant correlation between age and CCI. This analysis strongly confirmed the existence of such a statistically significant association ($p < 0.001$).

PCT levels (median (IQR)) showed a significant increase with disease severity, ranging from 2.45 (0.70–3.20) ng/mL for the "SIRS" group, 9.6 (6.3–12.2) ng/mL for the "sepsis" group, 24.7 (13.5–32.0) ng/mL for the "septic shock" group, and 32.0 (10.38–32.0) for the "deceased patients" group. This was found to be statistically significant for all groups ($p < 0.01$), as detailed in Table 1.

The SOFA score [median (IQR)] showed a significant upward trend consistent with the severity of the pathology, comprising 3.0 (2.0–4.0) for the "SIRS" group, 6.0 (4.0–7.0) for the "sepsis" group, 9.5 (8.0–12.0) for the "septic shock" group, and 10.0 (8.25–12.0) for the "deceased patients" group. Although this upward trend is obvious, the Mann-Whitney test failed to confirm it as statistically significant in the "sepsis" group ($p = 0.78$). For the other groups, the p-value was less than 0.001, indicating statistical significance (Table 1).

The same pattern can be seen in the qSOFA score, with higher median values (IQR) depending on the severity of the disease: 0.0 (0.0–0.0) for SIRS, 1.0 (0.0–1.75) for sepsis, 2.0 (2.0–3.0) for septic shock, and 3.0 (2.0–3.0) for the deceased patients, but without statistical

significance for the "sepsis" group (p = 0.32). In the case of the other groups, the p-value was less than 0.001, indicating statistical significance (Table 1).

The CCI [median (IQR)] was shown to increase in direct proportion to the stages of sepsis, being: 4.0 (1.0–8.0) for the "SIRS" group, 7.0 (3.0–9.0) for the "sepsis" group, 9.0 (7.0–12.0) for the "septic shock" group, and 11.0 (9.2–13.0) for the "deceased patients" group. This increase was statistically significant for all groups (p < 0.001), except for the "sepsis" group (p = 0.46) (Table 1).

The number of A&ICU care days needed to treat these patients was directly proportional to the severity of the cases. This aspect was found to be statistically significant for all groups (p < 0.001) (Table 1).

By analyzing the number of days of hospitalization (median (IQR)), an increasing trend can be observed in accordance with the severity of the disease: 5.0 (3.0–8.0) for SIRS, 9.0 (6.0–13.7) for sepsis, and 15.0 (8.0–22.5) for septic shock. This was not relevant for the "deceased patients" group [10.0 (6.25–18.7)] p = 0.22 (Table 1).

Increased hospitalization costs [median (IQR)] were found in the case of deceased patients [10,855.0 (6752.5–24,053.2) lei, p < 0.001] and those with septic shock [14,704.5 (7357.0–26,103.5) lei, p < 0.001]. In contrast, these costs were statistically significantly lower for patients with SIRS [2863.0 (1247.0–6833.0) Lei, p < 0.001] (Table 1). Given that the variables that describe the patient economically are theoretically interrelated, we used Spearman's correlation to assess whether this also applies to the patients in our study. Comparing intensive care days and hospitalization days with hospitalization costs, we obtained a result with p < 0.001 in both cases, thus confirming this hypothesis.

The predictability in identifying the cUTI stages was assessed using the area under the ROC (AUC) curve for each variable. All variables were compared with each other, one by one, for each group.
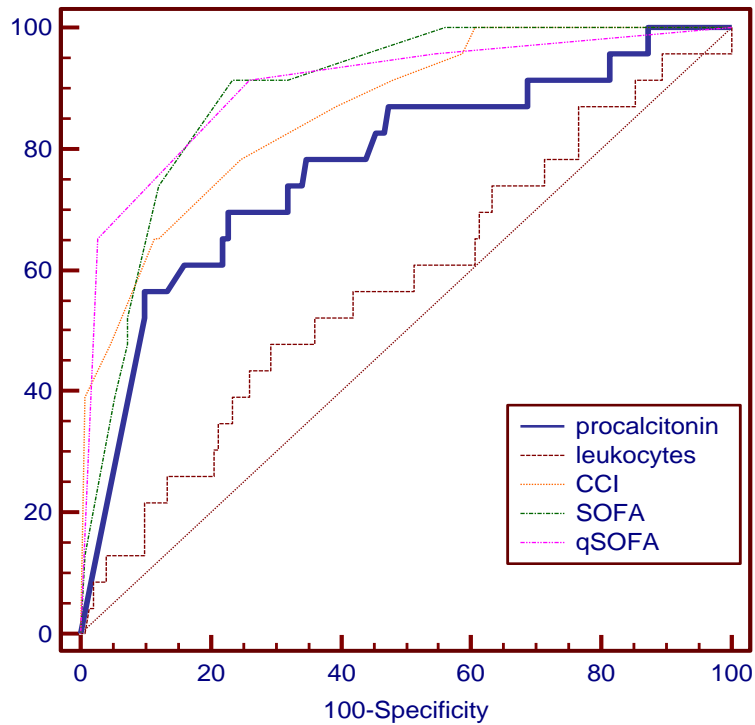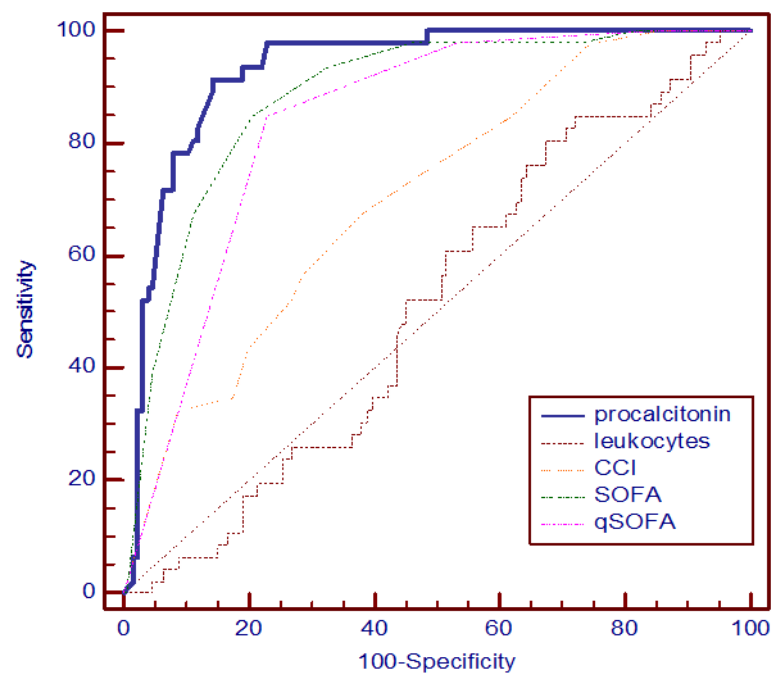
Figure 2. Comparison of ROC curves for the "deceased patients" group

The analysis of the ROC curves for the variables of interest in the "deceased patients" group highlighted the importance of these variables in predicting the risk of death. The PCT demonstrated a specificity of 69.57% and a sensitivity of 77.33%, indicating its ability to detect the risk of death early. The SOFA and qSOFA scores showed very high specificities, of 91.33% and 91.30%, and notable sensitivities of 76.82% and 74.17%, highlighting their usefulness as prognostic tools for patients at high risk of death. The CCI had a specificity of 65.22% and a sensitivity of 88.74%, highlighting its ability to identify patients with significant comorbidities at risk of death in the context of an acute event. The most significant result was obtained by the qSOFA score, with an AUC value of 90.3%, confirming its effectiveness in predicting the risk of death for patients with cUTI.

These findings underscore the fact that PCT, SOFA, qSOFA and CCI are essential and reliable variables for the prognosis of death risk in critically ill patients. The PCT stands out for its balance between specificity and sensitivity, being useful in the early detection of risk. SOFA and qSOFA, with their high specificities, are valuable tools for identifying high-risk patients, and CCI is particularly effective in detecting patients with comorbidities that can influence mortality. The qSOFA score, having the highest AUC value, proves to be the most effective in predicting the risk of death, making it a particularly valuable tool in the management of patients

with cUTIs. These variables can significantly improve the process of assessing and managing critically ill patients, contributing to more precise and effective interventions.

Figure 3. Comparison of ROC curves for the SIRS group

The study of patients with SIRS identified certain essential variables for diagnosis, with PCT standing out due to its specificity of 91.30% and sensitivity of 85.71%. These values indicate that PCT is very effective in correctly identifying patients with SIRS. The SOFA and qSOFA scores also had significant specificities of 84.78% and sensitivities of 78.74% and 76.34%, respectively, demonstrating their usefulness in diagnosis. The most relevant parameter for diagnosis was PCT, with a reference threshold of 4.8 and an AUC of 93%, confirming its accuracy in identifying patients with SIRS.

We note that PCT is an extremely valuable biomarker for the diagnosis of SIRS, due to its high specificity and sensitivity, which ensures the precise identification of affected patients. The SOFA and qSOFA scores contribute significantly to the diagnosis process, but the PCT stands out for its AUC value of 93%, emphasizing its superior ability to distinguish patients with SIRS. These findings underscore the critical importance of using PCT in the early and accurate diagnosis of SIRS, with the potential to transform the triage process and therapeutic strategies, which could lead to significant improvement in management and clinical outcomes for patients with SIRS.
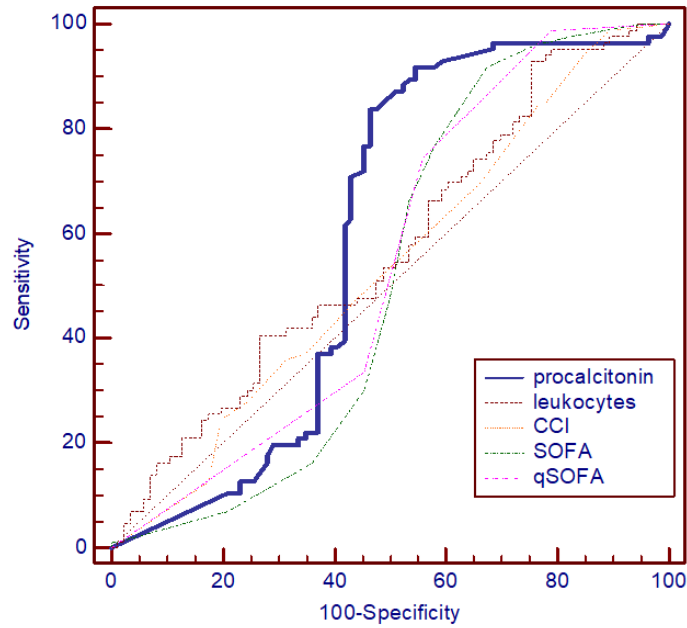
Figure 4. Comparison of ROC curves for the "sepsis" group

The results showed that, among patients with sepsis, only PCT provided statistically significant data for diagnosis. The PCT had an AUC value of 59.3%, specificity of 83.72%, and sensitivity of 53.49%, indicating it as an important biomarker in the diagnosis of sepsis. Other variables showed significant increases in specificity, but with a decrease in sensitivity.

Discussing these data, it is evident that PCT plays a vital role in diagnosing sepsis due to its high specificity, which helps in correctly identifying patients without sepsis. However, the sensitivity of 53.49% indicates that PCT can miss almost half of sepsis patients, highlighting the need for its use alongside other tools to increase diagnosis accuracy. The increase in specificity to other variables, accompanied by a decrease in sensitivity, shows the difficulty of finding markers that are both sensitive and specific.
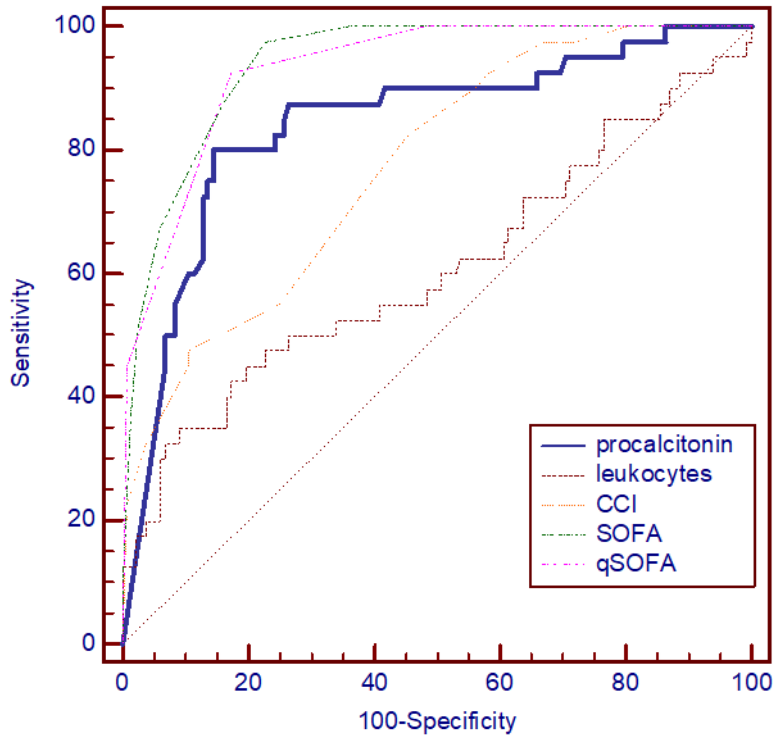
Figure 5. Comparison of ROC curves for the "septic shock" group

The research highlights the importance of using qSOFA and SOFA scores and PCT levels in the diagnosis and management of septic shock. The qSOFA score has a specificity of 92.5% and a sensitivity of 82.71%, being effective for the early identification of patients with septic shock. The SOFA score, with a specificity of 97.5% and a sensitivity of 77.44%, is crucial in assessing patients' condition and predicting risk, also demonstrated by the AUC of 93.9%. PCT levels, with a specificity of 80% and a sensitivity of 85.61%, are reliable in diagnosis. The combined use of these tools can significantly improve clinical outcomes.

We note that qSOFA and SOFA scores, along with monitoring PCT levels, provide a robust approach to the diagnosis and management of septic shock. qSOFA, with its high sensitivity and specificity, allows rapid identification of patients in the early stages of septic shock. The SOFA score, with an even higher specificity and an AUC value of 93.9%, is essential for a detailed and accurate assessment of patients' condition, being a solid predictor of disease severity. PCT levels complement these scores through their diagnosis ability, providing a clear picture of patients' inflammatory and infectious condition. Thus, the implementation of these tools in clinical practice can lead to faster and more effective interventions, significantly improving the prognosis of patients with septic shock.

4. Discussions

The clinical manifestation of UTI can include a wide range of presentations, from mild forms, such as simple cystitis, to severe manifestations, including septic shock or even death. In the context of daily medical practice, the rigorous assessment of the disease progression risk and the prompt intervention when the situation requires it [2] are issues of crucial importance. In this regard, there are several clinical tools and scores available for the assessment of patients with cUTI. In our study, we used validated scores, such as SOFA and qSOFA, to assess patients diagnosed with such infections [10,13]. We also used the CCI score to assess patients' performance status prior to these acute events [11], and the PCT biomarker to identify bacterial infections and their associated systemic impacts [8,9,14].

Notably, leukocyte counts were only marginally significant in assessing the patients diagnosed with cUTI and their risk of mortality. Although an increased number of leukocytes can serve as an alarm signal about the patient's clinical condition, they have only been shown to be a statistically significant indicator in patients in the "septic shock" group. However, they failed to provide notable accuracy in terms of differential diagnosis between SIRS and sepsis, which is an essential clinical distinction. In addition, when we compared the leukocytes with the other variables analyzed, they proved to be the least accurate indicator in defining the disease and its stage. This finding is particularly important given the tendency of clinicians to pay close attention to leukocyte levels in the evaluation of patients with sepsis.

In our analysis, we found that patients' age has a significant impact on the risk of developing septic shock and dying, with an increased risk associated with older age. An essential aspect to consider is the fact that age is a variable in the calculation of CCI, and elderly patients are theoretically more likely to develop comorbidities. Therefore, we assessed the correlation between age and CCI using the Spearman Rho correlation coefficient and obtained statistically significant results ($p < 0.001$), confirming a relevant correlation between these two variables.

It is important to note that the CCI was not initially designed for the evaluation of patients in the context of acute events, and this aspect was statistically confirmed when we tried to use it to distinguish between the stages of urosepsis. However, we clearly identified that an increased CCI value (with a threshold value of 10 and an AUC value of 86.3%) is associated with a higher probability of death. Thus, CCI proves to be an independent risk factor for mortality.

The team led by Yang started a study with the aim of investigating the evolutionary stages of sepsis and evaluating how useful CCI and age can be in predicting the risk of death

among hospitalized patients with sepsis. Their findings showed that advanced age and comorbidities are some of the most significant factors in determining in-hospital mortality and the use of medical resources [15]. Also, a retrospective multicenter study analyzed patients hospitalized with sepsis in intensive care units of 7 general hospitals in Israel over a period of 7 years and confirmed significant correlations between mortality and patient characteristics, including age and associated diseases [16].

Organ dysfunction is a factor associated with high morbidity and mortality rates [17] and, consequently, contributes significantly to the expenditure allocated to the A&ICU [18]. To assess organ dysfunction or multiorgan failure in dynamics and to assess the morbidity [19], organ failure assessment scores, such as the SOFA score, are used. Although this score was originally developed to describe and quantify organ function, and not to predict patient progression, numerous studies have demonstrated the obvious relationship between organ dysfunction and mortality [20,21]. The SOFA score is becoming increasingly relevant in defining both the patient's individual clinical status and response to therapy in the context of clinical trials [22]. It has been validated on large groups of patients and has been confirmed to be an independent predictor of mortality [23].

In our study, we found that the SOFA score was statistically significant and proved accurate in the positive diagnosis of SIRS and septic shock, becoming an independent predictor of mortality when a threshold value of 7 is reached. However, it should be noted that the SOFA score failed to classify patients in the "sepsis" group, as it showed a high specificity of 91.95% but a low sensitivity of 32.58%.

The qSOFA score, even though it includes a smaller number of variables and is based on the clinical assessment of patients, instead of relying on more accurate paraclinical data, could lead us to assume that it will have a lower sensitivity and specificity than those of the SOFA score. However, the results surprise us, indicating that the qSOFA score is similar to or even superior to the SOFA score in terms of its ability to predict mortality.

When trying to classify the patients in the "sepsis" group, the qSOFA score reveals the same limitations as the SOFA score. Although it maintains a high specificity of 98.85%, its sensitivity drops significantly to 20.93%.

These findings raise significant questions about the clinical efficacy and utility of the qSOFA score in terms of positive diagnosis of patients with sepsis and may suggest that a more complex approach is needed. Also, this analysis brings to our attention the need to investigate in depth the diagnosis approach and to develop more accurate tools for assessing the condition

of patients with cUTIs to manage more effectively improving the outcomes of these potentially critical patients.

The PCT, being a simple, affordable, and easy-to-perform test, has proven to be significant in terms of its ability to properly classify patients and to assess the evolutionary stage of urosepsis. A PCT level less than or equal to 4.8 stood out as having the greatest ability to exclude the diagnosis of urosepsis compared to the other variables, presenting a specificity of 91.30% and a sensitivity of 85.71%. At a reference value of 12.5, the PCT, with an AUC of 77.2%, proves to be a faithful predictor of mortality. Although it does not demonstrate a very high sensitivity (53.49%), PCT proves to be the most accurate variable for classifying patients in the "sepsis" group, presenting a specificity of 83.72% and an AUC of 59.3%.

PCT has the ability to accurately predict the presence of bacteremia and bacterial load in patients with cUTI [24]. Various studies have shown that a PCT level greater than 2 ng/mL has a specificity of more than 90% for sepsis or for the prognosis of progression to sepsis [25]. In our research, the threshold value for PCT in the identification of patients with sepsis was set at 4.8. It should be noted that PCT levels were higher in our study, possibly due to the prevalence of infections with Gram-negative organisms, which, compared to Gram-positive ones, cause higher PCT values [26]. Differences can also be attributed to varying observation periods, which can lead to different optimal PCT threshold values for diagnosing sepsis [27]. The variability can also be attributed to the different test kits and methods used in our study [28].

The "septic shock" group was relatively easy to diagnose, with SOFA, qSOFA and PCT proving high specificities and sensitivities. This is also true for deceased patients, where SOFA, qSOFA, PCT and CCI scores have been shown to be the independent predictors of mortality.

Analyzing all variables, a significant deficiency of the tools needed to classify patients in the "sepsis" group is observed. All variables have high specificity but low sensitivity. This translates into a risk of a false negative diagnosis, which can lead to a lack of appropriate treatment. Askim et al. concluded in their study that qSOFA failed to identify two-thirds of the patients admitted to the emergency department with sepsis and that it should not replace the traditional triage system [29]. One study aimed to assess the value of multiple disease severity scores for the prognostic assessment of sepsis; it concluded that SOFA and qSOFA scores cannot replace traditional assessment in patients at risk of developing sepsis [30]. Given that urosepsis is a pathology with possible serious repercussions, including death, and that there is a risk of incorrectly classifying patients with severe UTIs, we must act promptly. Appropriate initial antibiotic therapy (e.g., in the first hour) ensures an improved outcome in septic shock [31,32] and is also crucial in severe UTIs [33], as demonstrated in other infectious sites [34].

The empirical antibiotic therapy takes into account the expected bacterial spectrum, institutional-specific resistance rates, and individual patient requirements [35,36]. If the patient has associated an urinary tract pathology that complicates the patient's evolution, and here we refer to local favoring factors for the occurrence of cUTI, their control and/or elimination should be done within the first 6 hours [38].

Analyzing the above data, we observe that benign ureteral obstruction (n=79, 45.4%) and especially reno-ureteral lithiasis (n=63, 36.2%) represent the most common local risk factor for developing cUTI. However, patients with benign ureter obstruction tend to develop less severe forms of cUTI, being predisposed to manifest only SIRS (p=0.015, OR=2.23), and having a reduced risk of developing septic shock (p=0.001, OR=0.21) and death (p=0.001, OR=0.14). The same trend can be observed in patients with parenchymatous infection, with a predilection for developing SIRS (p=0.027, OR=2.47).

Diametrically opposite are patients who have been diagnosed with neoplastic invasion of the ureter (p=0.004, OR=0.15) and purulent collection (p=0.001, OR=0.13), as they tend not to be diagnosed with SIRS. They show a statistically significant association with septic shock, p=0.001, OR=3.70 in the case of those with neoplastic invasion of the ureter, respectively p=0.013, OR 2.74 in the case of purulent collections. Moreover, neoplastic obstruction of the ureter poses an intrinsic risk for death (p=0.001, OR=4.76).

Statistically, urosepsis is a burden on the health system, directly proportional to the severity of the case. Cases of septic shock are associated with an increase in hospitalization time and costs, also requiring additional days in the Intensive Care Unit. Sepsis is the biggest financial burden for hospitals and the leading cause of death in non-coronary intensive care cases, contributing to 30-50% of all hospital deaths [38]. Urosepsis is a severe urological condition with a significant mortality rate. The patient with cUTI should benefit from a complex clinical and paraclinical examination in a timely manner so that the correct diagnosis can be established and appropriate treatment can be received [39]. Given the fact that urosepsis is a pathology that can worsen, early diagnosis and treatment are imperative and can reduce hospitalization costs, as well as morbidity and mortality. The population should be educated about the implications of this pathology and encouraged to seek specialized help at the first symptoms of UTI [2,40].

Study II: Exploring the Dynamic Role of Bacterial Etiology in Complicated Urinary Tract Infections

1. Introduction

Urosepsis, as a serious manifestation of organ dysfunction induced by the abnormal response to an infection originating from the urinary tract or male genitalia, is a particularly delicate clinical situation. The progress towards urosepsis involves a complex succession of immunological events, amplifying the danger and the need for immediate therapeutic intervention [2]. This perspective emphasizes the essential balance between theoretical knowledge and practical skills to effectively manage patients with such critical conditions.

The standard definitions for the various categories of drug-resistant bacteria proposed by international organizations provide a clear framework for understanding antibiotic resistance. These classifications, such as Multiple Drug Resistance (MDR), "extremely" or "very extensive" Drug Resistance (XDR), and "Pan"-Drug Resistance (PDR), bring an opportune clarity to discussions about therapeutic strategies and management of antibiotic resistance [41].

Although the EAU (European Association of Urology) guidelines provide valuable guidance in the diagnosis and treatment of different forms of UTIs, there continue to be significant discrepancies globally in terms of pathogen spectrum, antibiotic resistance and the risk of progression to urosepsis [42]. This diversity shows the clinical complexity and specificity of each case, highlighting the need to adapt therapeutic protocols to the particularities of each medical environment.

Through this research, we aim to explore the bacterial etiology of cUTI and the bacterial resistance to antibiotics, with a focus on identifying a possible intrinsic risk associated with the development of urosepsis. This investigation not only aims to fill in the gaps in current knowledge, but also to provide practical information for improving the clinical approach and management of patients affected by this complex condition.

2. Material and method

We conducted a prospective study that included patients diagnosed with cUTI in the Urology Department of GCH, Romania. The research period covered the period from September 2019 to May 2022. GCH, with a capacity of 1220 beds, is located in the city of Galati and serves a resident population of approximately 250,000 inhabitants. It meets the health needs of Galati County, which has a total population of approximately 450,000 people.

The study received ethical approval from the Ethics Committee of GCH, Romania, under the reference number 24363/2021.

2.1. Patient selection

Inclusion criteria consisted of UTI confirmation based on urine culture and the presence of local or systemic risk factors associated with cUTI [43].

The following exclusion criteria were applied: patients diagnosed only based on clinical symptoms with no microbiological confirmation, under 18 years of age, pregnant women, history of kidney transplantation, hemodialysis or peritoneal dialysis and patients with missing data.

2.2. Data collection

Prior to admission, a comprehensive clinical assessment was performed, including various parameters: heart rate, blood pressure, respiratory rate, PaO_2, temperature, and Glasgow Coma Score. After admission, blood and urine samples were taken in accordance with International Safety Standards [44]. At the time of admission to the hospital, the blood count, total bilirubin, creatinine and PCT were determined.

The demographic information, clinical manifestations, laboratory findings, and diagnosis have been documented. A thorough examination of patients' medical records was carried out, extracting relevant clinical and biological data. We used CCI to assess the comorbidities that could predispose the patient to an immunocompromised status [11].

The identification of bacteria was based on a morphological evaluation of the colonies, as well as on biochemical characteristics such as lactose fermentation, indole production, urease activity, lysine decarboxylase activity, and hydrogen sulfide production [36]. The automatic Vitek system was used for identification in the cases where distinguishing between different types of Enterobacteriaceae involved difficulties [45].

The disc diffusion technique, carried out according to the guidelines of the Clinical Laboratory Standards Institute (CLSI), was used to determine the antimicrobial susceptibility of each bacterial strain.

2.3. Definition of patient groups

To assess the impact of bacterial resistance on clinical outcomes of patients with cUTI, including the risk of urosepsis and mortality, we divided patients into two distinct groups. The first group, called the non-MDR group, comprises patients who are resistant to less than three classes of antibiotics. Conversely, the second group, known as the MDR group, was made up of patients who showed resistance to three or more classes of antibiotics.

Based on the clinical and paraclinical presentation of the patients, while respecting the current definitions, we classified the patients into two other groups: those diagnosed with cUTI and those with urosepsis. The patients diagnosed with urosepsis were those who presented at admission or during hospitalization a cUTI proven by urine culture and SRIS.

The patients whose clinical picture progressed to septic shock and later died during hospitalization were included in a distinct group, called the "deceased patients" group.

2.4. Statistical analysis

The data were considered as nominal or quantitative variables. The nominal variables were characterized by frequencies. The quantitative variables were tested for normality of distribution using the Kolmogorov–Smirnov test and were characterized by median and minimum-maximum range or by mean and SD, when applicable. The chi-square test was used to compare the frequencies of nominal variables. The quantitative variables were compared using the Student's t-test or the Mann–Whitney U test, when appropriate.

The level of statistical significance was set at $p < 0.05$. The statistical analysis was performed using SPSS for Windows, version 23.0 (SPSS, Inc., Chicago, IL, USA).

3. Results

During the time we had conducted the study, 174 patients diagnosed with cUTI and urosepsis had been admitted to the Urology Department of GCH. Of these, only 102 had microbiological confirmation and were included in this study. Of the 72 patients with clinically confirmed infection only: 28 had sterile urine culture, most likely in the context of antibiotic therapy administered in the pre-hospital; 24 had mixed microbial flora, probably due to incorrect collection and 10 patients did not have the sample collected for urine culture (Figure 6).
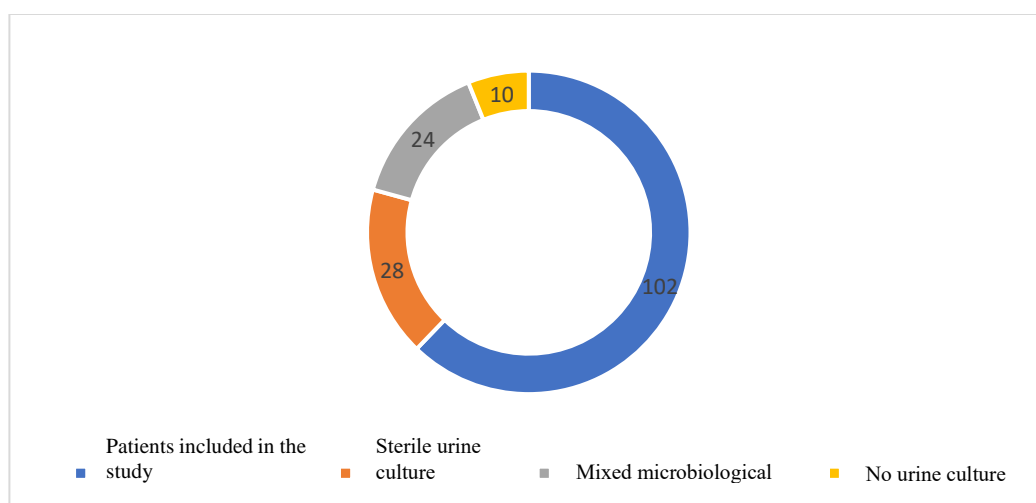
**Figure 6.** Patients included in the study

Examining the age of patients according to their decade of life revealed an increased incidence of cUTI with age. The mean age was 60.78 years with an SD of 15.99. Of the total patients, 33 were female, representing 32.35%. 37 patients came from rural areas, representing 36.27% of the total.

Depending on the clinical status of the patients, 64 patients, representing 62.75%, were diagnosed with urosepsis, the rest being included in the cUTI group. Of the entire cohort of patients, a total of 14 individuals, representing a proportion of 13.72%, died during their hospital stay (Figure 7).
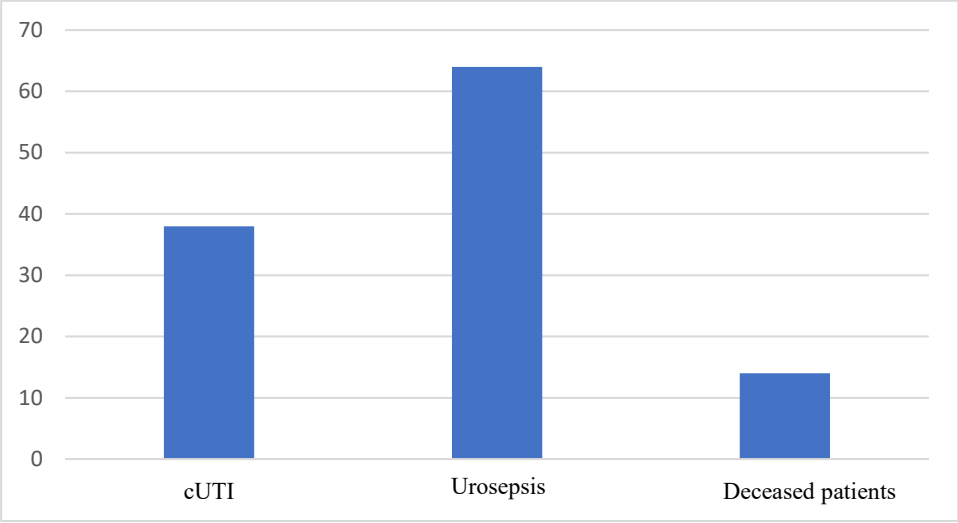
Figure 7. Classification of patients into diagnostic groups

A significant number of patients, respectively 41 (40.2%), were diagnosed with MDR infections, reflecting the complexity and importance of this clinical condition (Figure 8).
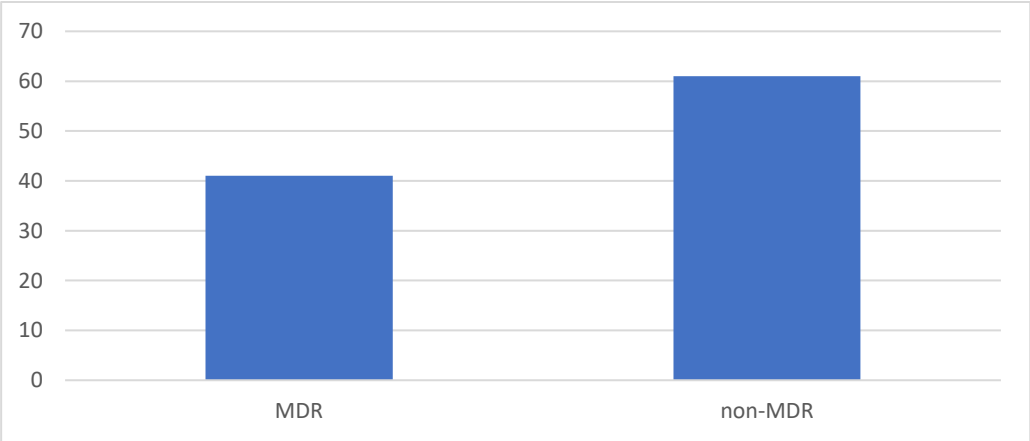

Figure 8. Classification of bacteria into groups according to antibiotic resistance

Of the total number of patients enrolled in our study, a subgroup of 32 people, representing 31.37%, was identified as a chronic urinary catheter carrier, including urethro-bladder catheters, cystostomies, ureteral splints and stents, as well as nephrostomies.

From the bacteriological etiological perspective, *E. coli* was identified as the predominant pathogen, affecting 51 patients, and representing a significant proportion of 50% of the investigated cases. It should be noted that *Klebsiella spp.* manifested itself as a causative agent in 27 cases, representing a significant proportion of 26.47%. Presence of *Enterococcus spp.* was documented in 13 patients (12.74%), while *Pseudomonas* appeared as an etiological factor in the clinical context of eight patients (7.8%). It is important to note that one infection caused by *Proteus* was reported in two patients, while another patient developed an infection caused by *beta-hemolytic Streptococcus* (Figure 9).
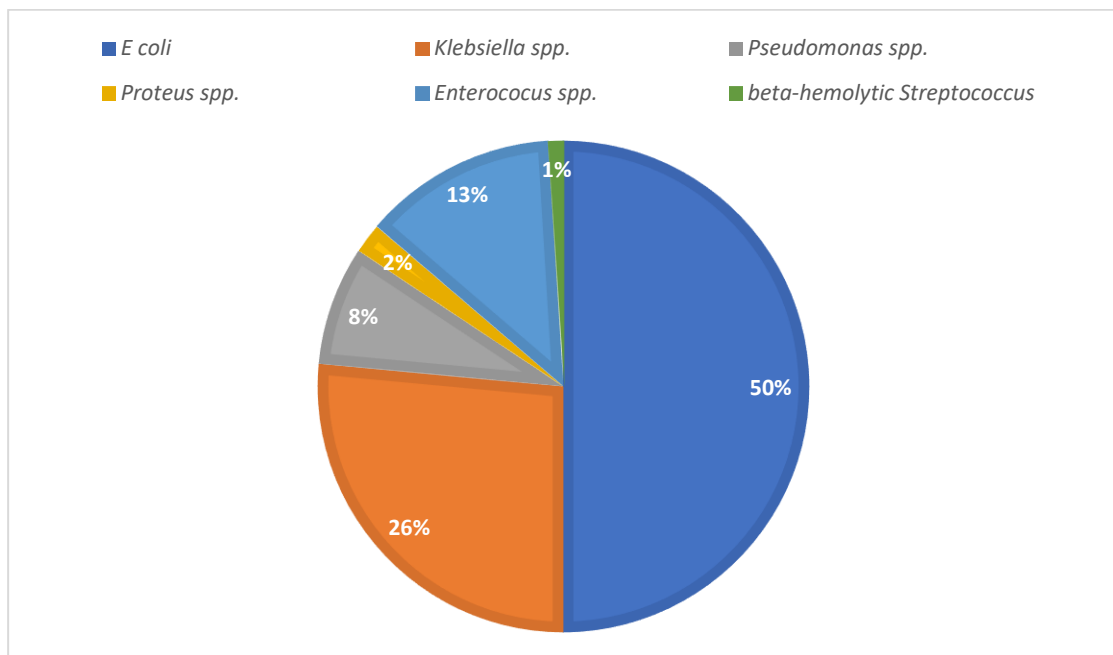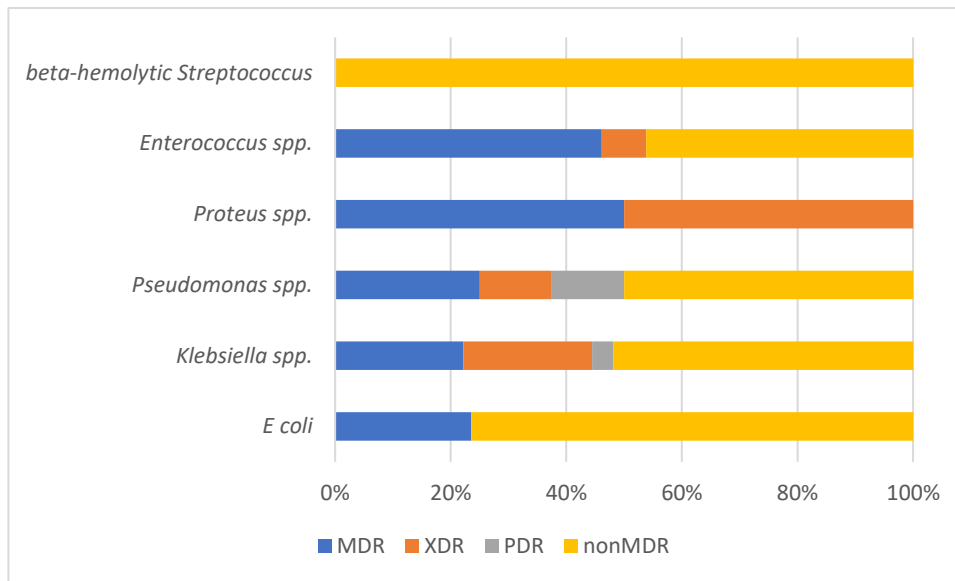

Figure 9. Bacterial etiology

Remarkable conclusions stand out when examining the antibiotic resistance independently of the specific type of microorganisms. Of particular concern is the growing resistance to penicillins, ampicillin showing a remarkably high resistance rate of 74.5%. Similarly, the trimethoprim-sulfamethoxazole combination elicits considerable resistance, with bacteria showing a prevalence of resistance of 58.82%. Fluoroquinolones, ciprofloxacin, and levofloxacin face a significant barrier, showing resistance rates of 49% and 37.25%, respectively. It is worth noting that cephalosporins show a consistent pattern of resistance, with a gradual downward trend in successive generations. Specifically, first-generation cephalosporins exhibit a resistance rate of 35.29%, followed by 32.35% for the second generation, 31.37% for the third generation, and a relatively lower resistance rate of 24.5% for the fourth generation, represented by Cefepime. The emergence of resistance is also found in the case of amikacin and tigecycline, affecting 12.75% of the bacterial population. In the case

of carbapenems, a similar resistance profile is observed, with meropenem and ertapenem showing a parallel resistance rate of 11.76%. However, it is worth mentioning that piperacillin–tazobactam stands out as a powerful therapeutic resource, as only 9.8% of the bacterial strains studied showed resistance to this combination (Figure 10).
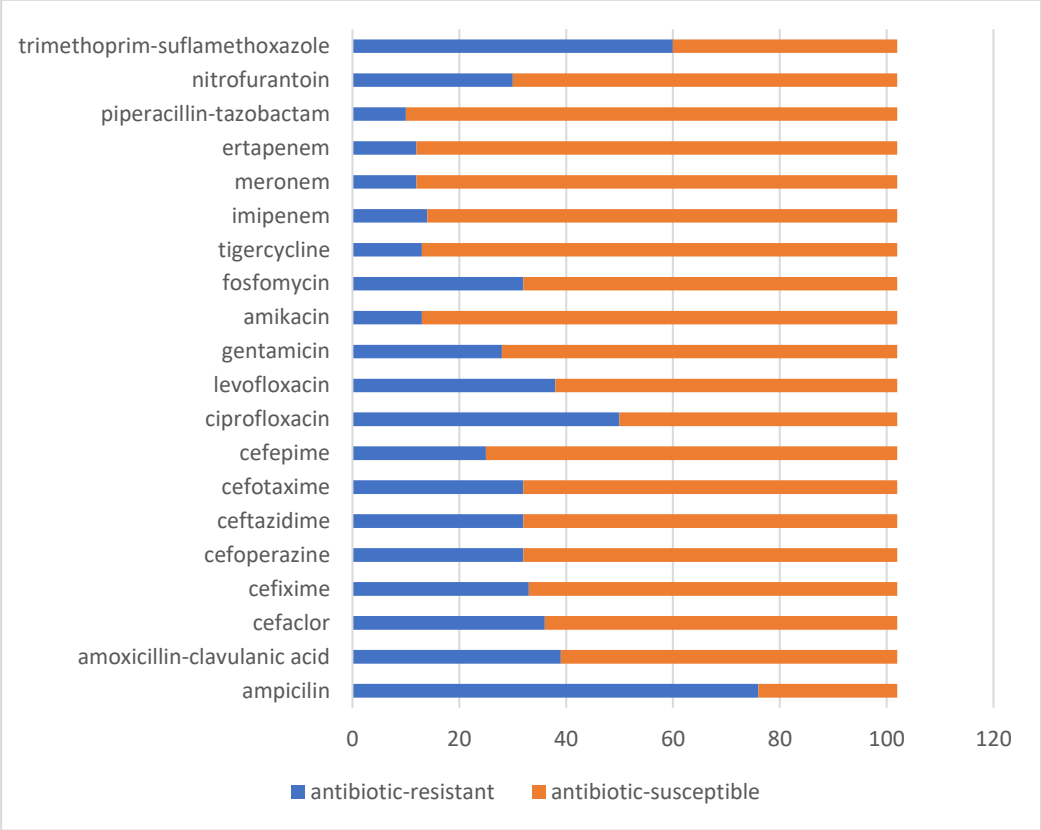
Figure 10. Bacterial resistance to antibiotics

By examining the antibiotic resistance profile for each bacterial species individually, distinctive patterns become evident. Particularly significant is the observation within the *E. coli* species, where a subgroup of 12 strains, representing 23.53% of the cases, presents the MDR phenotype. As for patients diagnosed with *Klebsiella* infections, a significant proportion of 13 people, representing 48.14%, presented the worrying development of MDR infection. Among these patients, a notable subgroup of 6 people, consisting of 22.22% of the total, was found to have an XDR infection, while only one patient (3.7%) manifested the alarming PDR phenotype. In the case of *Enterococcus* strains, an important finding resulted, with 7 cases representing 53.84%, demonstrating the MDR phenotype. As for *Pseudomonas infections*, 50% are classified as MDR, with one strain identified as XDR and another strain identified as PDR. Our study included only 2 patients who developed *Proteus* infection. All these bacterial strains have been identified as MDR, with one of them classified as XDR (Figure 11).

Figure 11. MDR status according to bacterial etiology

The Chi-square test was used to highlight the correlation between the presence of MDR infection and the existence of indwelling urinary catheters, resulting in a p-value of 0.002, signifying a statistically significant interdependence. The Chi-square test was used to assess whether MDR infection represents an intrinsic risk factor for mortality, generating a p-value of 0.048, establishing the statistical significance of this association. Using the same test, we examined whether there is a correlation between MDR infection and the risk of developing urosepsis. The resulting p-value of 0.199 suggests that there is no significant interdependence between the two variables. In the same context, it has been shown that there are no correlations between gender and the environment of origin and the risk of developing MDR infection (Table 29).

By using the Mann-Whitney U test, we evaluated the interdependence between comorbidities, represented by CCI, and MDR infection, resulting in a p-value below 0.001 and thus confirming this hypothesis. Using the Student's t-test, we analyzed the correlation between age and the risk of developing MDR infection, obtaining a p-value below 0.001 and thus demonstrating this interdependence (Table 29). Similarly, the same test was applied to assess the correlation between age and the existence of indwelling urinary catheters, generating a p-value < 0.001, indicating a strong correlation between these two variables (Table 2).

Table 2. Bivariate analysis of variables according to MDR status

	All patients (n-102)	Non-MDR (n-61)	MDR (n-41)	P-value
Age (years), mean+/- SD	60.78=/-15.996	55.07+/-15.616	69.29 +/- 12.498	0.0001**
medium, urban (n, %)	65 (63.7)	42 (68.9)	23 (56.1)	0.18*
Sex, male (n, %)	69 (67.6)	37 (60.7)	32 (78.0)	p=0.066*
CCI (median-min-max)	7-0-13	4-0-13	8-1-13	p=0.004***
Deceased (n, %)	14 (13.7)	5 (8.2)	9 (22.0)	p=0.048*
Urinary catheter (n, %)	32 (31.4)	12 (19.7)	20 (48.8)	p=0.002*
Urosepsis (n, %)	64 (64.7)	36 (59.0)	26 (63.4)	p=0.199*

To highlight whether there is a correlation between the bacterial etiology of cUTI and the risk of developing urosepsis, we used the Chi-square test. We performed an analysis on the bacteria that were most frequently encountered. No statistically significant correlation was found for *E. coli* (p = 0.41), *Klebsiella* (p = 0.06) or *Enterococcus* (p = 0.60). *Pseudomonas infection* has been shown to be a protective factor against the development of urosepsis (p = 0.021, OR = 0.171) (Table 3).

Table 3. Bivariate analysis of bacterial species according to diagnosis

	All patients (n-102)	cUTI (n-38)	Urosepsis (N-64)	p-value*	OR (CI 95%)
E coli (n, %)	51 (50)	21 (55.3)	30 (46.9)	0.41	0.71 (32-160)
Klebsiella (n, %)	27 (26.5)	6 (15.8)	21 (32.8)	0.06	2.6 (94-71.9)
Enterococcus (n, %)	13 (12.7)	4 (10.5)	9 (14.1)	0.60	1.39 (39-486)
Pseudomonas (n, %)	8 (7.8)	6 (15.8)	2 (3.1)	0.021	0.172 (33-90)

*Chi-square test; OR-relative risk; CI-confidence interval

Table 4. Bivariate analysis of bacterial species according to MDR status

	All patients (n-102)	Non-MDR (N-61)	MDR (N-41)	p-value*	OR (CI 95%)
E coli (n, %)	51 (50)	39 (62.9)	12 (29.3)	0.001	0.233 (10.0-54.0)
Klebsiella spp. (n, %)	27 (26.5)	12 (19.7)	15 (36.6)	0.058	2.356 (9.6-57.7)
Enterococcus spp. (n, %)	13 (12.7)	6 (9.8)	7 (17.1)	0.283	1.887 (58.5-60.88)
Pseudomonas spp. (n, %)	8 (7.8)	3 (4.9%)	5 (12.2%)	0.180	2.685 (60.5-119.2)

*Chi-square test; OR-relative risk; CI-confidence interval

To investigate whether cUTI is a risk factor for MDR according to bacterial etiology, we used the Chi-square test. An analysis was carried out on the most frequently encountered bacteria. E. *coli* infection has been shown to be a protective factor against antibiotic resistance (p = 0.001, OR 0.233). The other bacterial etiologies did not show a statistically significant association with MDR infection (Table 4).

4. Discussions

In our study, the average age of patients was 60.78 ± 15.99 years. This finding supports the idea that cUTI is a condition with an increased prevalence associated with aging. We consider that pathologies associated with old age act as risk factors for the development of cUTI, as statistically demonstrated by the Spearman Rho correlation test (p < 0.001). In addition, there is a significant age-related dependence on the risk of developing an MDR infection (p < 0.001). This observation receives further support from the statistically significant correlation between aging and the use of permanent urinary drainage devices (p < 0.001), as well as the remarkable association between urinary devices and increased susceptibility to MDR infections (p = 0.002). Atiyah et al. concluded in their paper that the increasing use of indwelling catheters has led to a significant number of complications, with infection being the most common. Pathogens responsible for urinary tract infections form biofilms on the surfaces of medical devices, allowing them to evade the host body's defenses and develop resistance to antimicrobial agents [46]. In a 2016 study involving a cohort of 585 patients diagnosed with urosepsis, a significant association was found between the use of indwelling urinary catheters, the presence of comorbidities and older age, and an increased incidence of MDR infections, ultimately leading to increased vulnerability in the development of septic shock [47].

The observed prevalence of MDR infections in our study (40.2%) exceeds the rates reported in the existing literature. This disparity can be attributed mainly to the distinctive attributes of our study sample, which included elderly patients with multiple comorbidities and an extensive history of drug treatment, including antibiotic therapy [48]. Strains of *E. coli* isolates from patients with urosepsis show a lower prevalence of genetic characteristics that are phenotypically translated into virulence and are less likely to originate from an uropathogenic type than strains isolated from patients with uncomplicated UTIs. Organisms isolated from cUTI and urosepsis tend to be more resistant to antibiotics than strains isolated in simple UTIs [49].

In our study, we found no evidence of a statistically significant association (p = 0.199) between MDR infection and the risk of developing urosepsis. This finding is consistent with the conclusions drawn by Shaw et al., who conducted a separate study and determined that host factors, rather than specific microorganisms or patterns of antimicrobial resistance, mainly influence the occurrence of urosepsis [50]. However, MDR infection was established as a standalone risk factor for mortality (p = 0.048). It is recognized that patients affected by MDR infections frequently have several comorbidities. Moreover, there is a significant correlation between infection resistant to multiple antibiotics and the administration of inadequate empirical therapy. While some studies highlight MDR infection as an independent risk factor for mortality, others emphasize its role as a risk factor for inadequate antibiotic therapy. The latter, in turn, is identified as an independent risk factor for mortality [51,52].

In the study, *E. coli* showed the highest prevalence, covering 50% of cases, followed by *Klebsiella* in a proportion of 26.47%. *Enterococcus* and *Pseudomonas* were also identified, accounting for 12.74% and 7.8% of cases, respectively. The literature indicates that Gram-negative bacteria have been identified as predominant etiological agents, contributing to most cases of UTIs. The distribution of Gram-negative bacteria in the cohort analyzed by Wagenlehner et al. in 2007 was as follows: E. coli accounted for 50% of cases, while *Proteus spp., Enterobacter and Klebsiella* contributed together with 15% of the cases. *Pseudomonas aeruginosa* has been identified as a causative factor in 5% of cases [53]. The microbial landscape of cUTI is heterogeneous, encompassing a diverse range of Gram-negative and Gram-positive bacterial species. This spectrum of bacteria can highlight geographical variations, temporal fluctuations and intra-institutional disparities even within the same health unit [54-56]. It is of particular importance for each healthcare facility to establish a comprehensive surveillance system to accurately document urinary tract infections, focusing

specifically on cUTIs and nosocomial UTIs. This meticulous record allows for an individualized and tailored approach in the management of these infections.

When assessing the possibility that the bacterial etiology poses an intrinsic risk for the development of urosepsis, the most common bacteria did not show statistical significance. In contrast, *Pseudomonas* stood out as a protective factor against the development of urosepsis (p = 0.021, OR = 0.171). This suggests that cUTIs caused by this specific etiological agent have a lower risk of progressing to urosepsis. However, given that there are only eight cases (7.8%) of *Pseudomonas* infections in our cohort, we cannot extrapolate this result with confidence. Further investigation on larger patient groups will be necessary to validate this finding.

In terms of antibiotic resistance, our study focused on patients with UTIs and urosepsis, many of whom had significant comorbidities, advanced age, and indwelling urinary catheters. We identified a significant prevalence of resistance to first-line antibiotics. Specifically, penicillins showed an overall resistance rate of 74.5%, with *Klebsiella* strains exhibiting intrinsic resistance to ampicillin (100%). Furthermore, we identified high resistance rates: 58.82% for trimethoprim-sulfamethoxazole and 49% for fluoroquinolones, including ciprofloxacin, while levofloxacin showed a resistance rate of 37.25%. Specifically, cephalosporin resistance showed an inverse correlation with the antibiotic generation, with fourth generation cephalosporins showing a resistance rate of 24.5%, and first-generation cephalosporins a resistance rate of 35.29%. According to the findings of our study, in order to achieve the desired therapeutic effect using the principle of escalation in antibiotic therapy for patients with urosepsis, these aforementioned antibiotics should be excluded, with the possible exception of fourth generation cephalosporins. Antibiotics that demonstrated low rates of resistance included amikacin, tigecycline (12.75%), carbapenems (11.76%), and piperacillin-tazobactam (9.8%). These antibiotics should be considered in the treatment of a patient with urosepsis with a potentially poor prognosis until the result of the antibiogram is obtained.

A study conducted in Romania in 2018, involving 916 patients diagnosed with UTIs, identified *E. coli* as the main etiological agent, with a prevalence of 42.9%, followed by *Enterococcus faecalis*, with a prevalence of 21.17%, and *Klebsiella spp.*, with a prevalence of 18.66%. This research revealed antibiotic resistance rates for Levofloxacin that exceeded 30% in the case of *E. coli* and over 40% for *Enterococcus*. It was also found that the strains of *Klebsiella* had developed significant resistance to carbapenems and aminoglycosides, with a prevalence of more than 10%. Although the resistance rates reported in this study are alarming, it should be noted that they are lower compared to those found in our research. It is important to emphasize that the study in Romania included all UTIs, while our research focused

exclusively on the cUTI analysis. This distinction reinforces the idea that the same empirical antibiotic treatment protocol should not be applied for cUTIs as in the case of simple UTIs [57,58].

Bischoff's research identifies specific risk factors related to antibiotic resistance in UTIs. These risk factors align with conditions that increase a person's susceptibility to cUTIs. The study suggests that in cases where these risk factors are lacking, cephalosporins are a suitable choice for empirical therapy. However, for patients with these risk factors, piperacillin-tazobactam may be a superior therapeutic alternative to fluoroquinolones, cephalosporins or gentamicin. This study highlights the importance of local surveillance of resistance rates and risk factors for optimizing empirical therapy in a specific geographic context [59].

In 2019, Jiang et al. published a retrospective study that looked at 94 patients diagnosed with urosepsis. The main etiological agent identified was *E. coli* (64.62%), followed by *Klebsiella spp.* (21.84%). The study showed a resistance rate exceeding 80% for penicillins, first- to third-generation cephalosporins, and quinolones, with a susceptibility of 50% for aminoglycosides and 100% for carbapenems [60].

The Global Prevalence of Infections in Urology is a study conducted by Tandogdu and his colleagues, which includes patients admitted to urology departments around the world. The study assesses healthcare-associated infections and their risk of progressing to urosepsis. The most commonly identified pathogen is *E. coli* (43%), followed by *Enterococcus spp.*, *Pseudomonas aeruginosa* and *Klebsiella spp.* An MDR rate of 45% has been reported for *Enterobacteriaceae*. The only class of antibiotics that showed a resistance rate of less than 10% were carbapenems [61].

Given the fact that MDR bacteria are more frequently encountered as etiological agents in the case of cUTI and urosepsis, including resistance to carbapenems, Chen lists as potential therapeutic resources, in this regard, polymyxins, fosfomycin, tigecycline, nitrofurantoin, linezolid and daptomycin. However, it is imperative to emphasize that this conclusion requires further study [61]. Similarly, in a study by Lee et al., it was concluded that in the management of UTI patients who meet the criteria for critical sepsis at baseline, it is advisable to consider empirically prescribing broad-spectrum antibiotics capable of addressing potential patterns of drug resistance. Such antibiotics may include tigecycline, carbapenems, or fourth generation cephalosporins [62].

To fully understand the antibiotic resistance profiles of each bacterial species comprehensively, significant proportions of MDR cases are observed for *Proteus* (100%), *Enterococcus* (53.86%) and *Pseudomonas* (50%). However, given the relatively low prevalence

of these bacteria in our study, it is not feasible to make meaningful comparisons and determine their impact on the progression of cUTI in our geographic area. To improve understanding, this study would benefit from the inclusion of a larger and more diverse database with a larger number of subjects collected prospectively over an extended period. Analyzing whether bacterial species involved in cUTI carry an individual risk of being MDR, we identified that *E. coli* has a lower risk of being MDR (p = 0.001, OR 0.233). This indicates that *E. coli* infections are more likely to be acquired in the community and not associated with the medical environment [63]. The same conclusion can be drawn from the results analyzed and published in 2018 by the European Center for Disease Prevention and Control (ECDC) on antibiotic resistance in *E. coli* (e.g., 22.8% for third generation cephalosporins and 0% for carbapenems) in Romania [13]. This report also highlights the MDR rate in infections caused by *Klebsilla spp.* (e.g., 67.3% for third generation cephalosporins and 20.5% for carbapenems) in our country, along with the future risk of lacking therapeutic solutions for the management of infections caused by this pathogen [13]. Our study also highlights the concerning aspect residing in the fact that *Klebsiella*, as the prevalent pathogen in more than a quarter of cases, exhibits a significant MDR rate of 48.14%. In these cases, a significant subset of 22.22% exhibit XDR characteristics, while a further 3.7% demonstrate the alarming PDR phenotype. *Klebsiella* is the second most common etiologic agent, but shows significant resistance to first-line antibiotics, as previously demonstrated by Mishra in India [32] and Petca in Romania [26]. It is imperative to carry out further investigations to establish the possible association of this strain with healthcare-associated infections and to implement proactive strategies aimed at reducing its transmission dynamics.

Chapter III. CONCLUSIONS

This paper provides valuable insights into the complexity of cUTI and the challenges associated with the diagnosis and management of urosepsis. Urinary tract infections can range from simple cystitis to septic shock and death, highlighting the importance of a quick and accurate assessment of the risk of disease progression. Our study makes essential contributions to the understanding and optimization of using clinical tools in the assessment of these patients.

We demonstrated that although the SOFA and qSOFA scores are useful for assessing organ dysfunction and response to therapy, they have significant limitations in the classification of patients with urosepsis, having a low sensitivity. However, both scores proved to be independent predictors of mortality, qSOFA even providing superior specificity in this context. It highlights the need not to replace traditional triage systems with these scores, but to use them in a complementary way to avoid the risk of a false negative diagnosis, which could lead to a lack of appropriate treatment.

In contrast, PCT stood out as a particularly valuable marker in discriminating patients with urosepsis, having the ability to correctly classify patients according to disease severity. High levels of PCT were associated with the presence of bacteremia and bacterial load, and its specificity and sensitivity, although not perfect, are superior to the other variables studied. This finding underlines the potential of PCT to become a central element in the diagnosis and treatment protocols of urosepsis.

On the other hand, our analysis highlighted the significant correlation between advanced age, high CCI value and mortality. Elderly patients and those with multiple comorbidities are at increased risk of developing septic shock and death. Although CCI was not originally developed for the assessment of acute events, this study confirms that a high CCI value is an independent risk factor for mortality in the context of urosepsis. This information is crucial for personalizing treatment and allocating clinical resources, ensuring appropriate and prompt intervention.

A significant correlation between advanced age, the presence of comorbidities and an increased risk of developing MDR infections has been highlighted in the research. In addition, the use of indwelling urinary catheters has been shown to be a major factor in increasing susceptibility to these infections, highlighting the need for strict infection control measures in healthcare facilities. The study did not demonstrate a significant link between MDR infections and the risk of developing urosepsis, suggesting that host factors play a more important role in

this progression, but at the same time infection with MDR phenotypes is proving to be a risk factor for mortality.

Bacterial spectrum analysis revealed the predominance of Gram-negative bacteria, especially *E. coli*, as the main etiological agent, followed by *Klebsiella spp.*, which showed high resistance to first-line antibiotics. Local monitoring of bacterial resistance is very important for optimizing empirical treatments. In the context of the increasing prevalence of multidrug-resistant bacterial strains, including those with XDR and PDR phenotypes, it is imperative to develop proactive strategies to control and prevent the spread of these pathogens, thus ensuring effective management of cUTI and urosepsis. For empirical antibiotic treatment in patients with cUTI who are at high risk of developing urosepsis and having a potentially adverse clinical course, broad-spectrum antibiotic therapy is recommended. This may include antibiotics such as amikacin, tigecycline, carbapenems, and piperacillin–tazobactam.

From an economic and public health point of view, urosepsis represents a significant burden on the health system, associated with increased hospitalization time, costs and the need for care in intensive care units. Sepsis remains one of the leading causes of death in non-coronary intensive care units, contributing to a considerable proportion of all hospital deaths. Thus, early diagnosis and treatment of urosepsis can not only reduce mortality and morbidity but can also significantly reduce the costs associated with the treatment of this severe condition.

The study highlights the urgent need to improve the approach to the diagnosis and treatment of patients with cUTI and urosepsis. Current tools, while valuable, need to be used in combination and complemented with additional biomarkers, such as PCT, to ensure a complete and accurate assessment. Educating the population about the risks of this pathology and encouraging medical consultation at the first symptoms of UTI are also imperative to reduce the incidence and severity of urosepsis cases.

Chapter IV. ORIGINALITY OF THE THESIS

This doctoral thesis represents a significant contribution in the medical field, especially in the management of cUTI and urosepsis, addressing critical challenges that directly influence the medical act and therapeutic outcomes. The prospective study, which had been carried out over four years at the Galati County Hospital, not only explores the specificity and characteristics of infections in this region, but also proposes new paradigms for the diagnosis and effective management of these serious conditions, with a profound impact on public health.

In particular, the thesis highlights the major limitations of the SOFA and qSOFA scores, widely used instruments for assessing the severity of sepsis. Although these scores are useful for prognosticating the evolution of patients admitted to intensive care units, they are not accurate enough to allow an early and effective diagnosis of sepsis in the initial phase of triage. This finding underscores the urgent need to reassess current protocols and develop additional methods for early identification of sepsis, with the aim of saving lives and improving therapeutic outcomes.

On the other hand, the introduction of PCT as a central biomarker in the assessment and management of sepsis represents an innovative discovery, with the potential to fundamentally transform the medical approach to this condition. PCT has been shown to be not only a sensitive and specific marker for severe bacterial infections, but also a reliable predictor of mortality. It opens new horizons in the early diagnosis of sepsis, allowing for rapid and targeted interventions with a significant impact on patient survival.

Moreover, the thesis makes an essential contribution to understanding the risks associated with comorbidities and other predisposing factors in patients with cUTIs. By highlighting the fact that patients with a high CCI score have an increased risk of mortality during an acute infectious event, the paper highlights the importance of a personalized and more aggressive approach in the treatment of these patients. This includes both rigorous clinical evaluation and early initiation of antimicrobial treatment, thus ensuring close monitoring and adaptation of therapy according to the course of the disease.

Regarding the challenge of infections with MDR bacteria, the thesis provides a detailed analysis of the risk factors and therapeutic strategies needed to combat this growing phenomenon. The identification of advanced age, comorbidities, and the use of indwelling urinary catheters as key factors in the development of MDR infections underlines the need for judicious administration of antibiotics, especially broad-spectrum ones. Through the rational use of antimicrobial agents, such as amikacin, tigecycline, carbapenems and piperacillin-

tazobactam, the thesis contributes to the development of more effective treatment protocols better adapted to the needs of each patient.

In conclusion, this thesis not only enriches the existing knowledge in the medical field, but also provides concrete and applicable solutions to the current challenges in the management of sepsis and cUTI. The implementation of the conclusions and recommendations presented in this paper can lead to a significant improvement in standards of care, a reduction in mortality rates and the optimization of medical resources, thus having a profound impact on the quality of life of patients and on the efficiency of the health system globally.
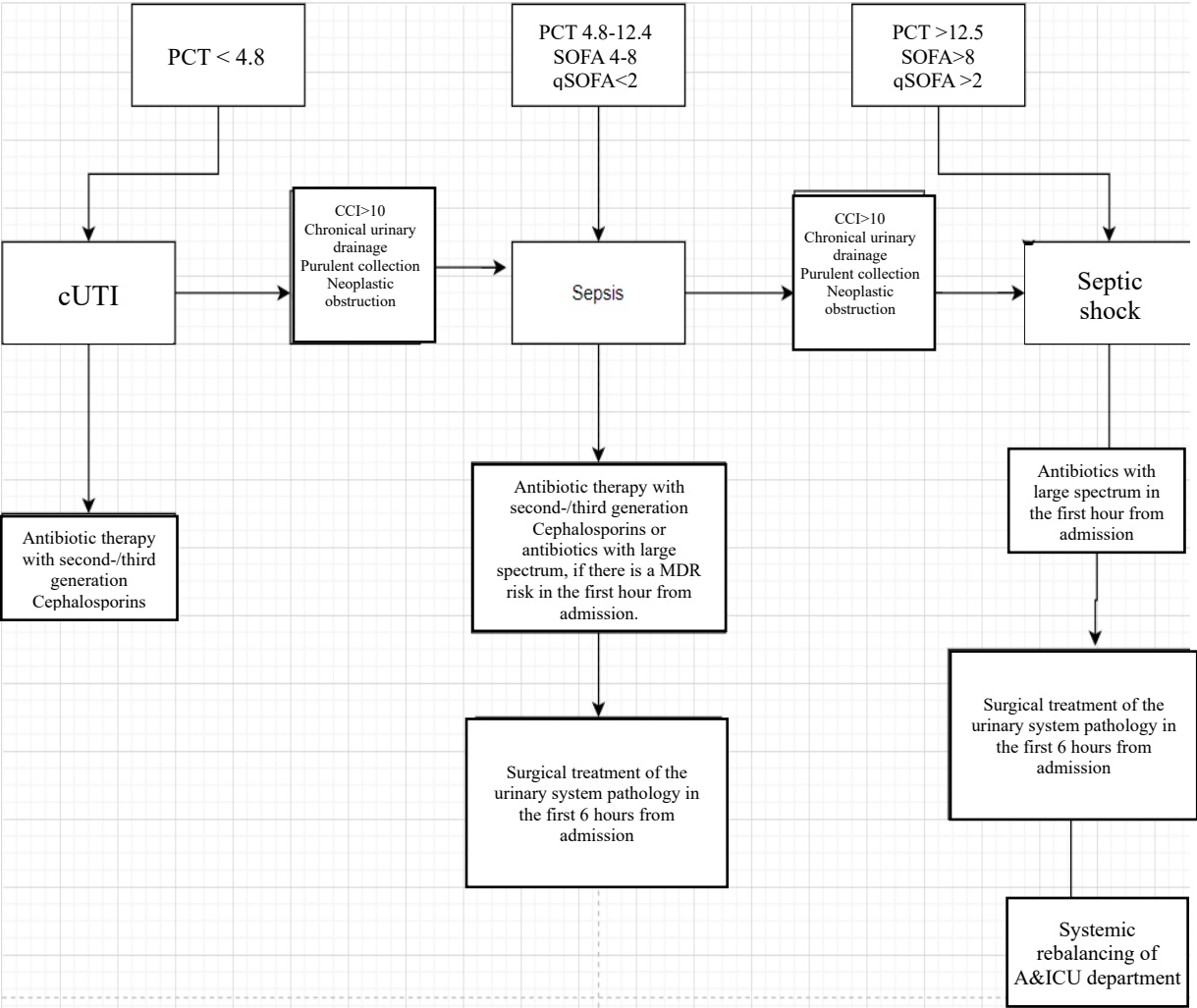

Figure 12. Urosepsis management protocol

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