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ORIGINAL RESEARCH

The Risk of Death among Patients with Healthcare-associated Infections and Cardiovascular Diseases Admitted to the Intensive Care Unit in Romania

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ABSTRACT

Background: Healthcare-associated infections (HAIs) can pose significant risks to patients with cardiovascular disease due to the compromised nature of their health and potential vulnerabilities. In order to reduce the incidence of HAIs and prevent the spread of antibiotic-resistant organisms, it is mandatory to develop surveillance systems. **Methods:** We undertook a retrospective case–control study of all patients presenting HAIs who were admitted to the intensive care unit (ICU) to assess risk factors associated with death among patients with cardiovascular disease. **Results:** Patients admitted to the ICU who died were more likely to present an infection with a multidrug-resistant bacterium, an infection with *Acinetobacter baumannii*, and to suffer from acute myocardial infarction. Among the patients enrolled in the study, a higher probability of death was also observed in association with certain Gram-negative pathogens such as *Klebsiella pneumoniae*, *Acinetobacter baumannii*, and *Pseudomonas aeruginosa*. **Conclusion:** The longer the patient remains admitted in the ICU, the higher the risk of acquiring an infection that can often become fatal. A nosocomial infection, particularly in patients with cardiovascular disease, also increases the length of hospitalization, which will lead to increased expenditure. For this reason, new prophylactic methods and therapeutic approaches are needed, and researchers' efforts should be directed in this direction.

Keywords: healthcare-associated infections, intensive care unit, cardiovascular diseases, multidrug-resistant bacteria

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INTRODUCTION

Cardiovascular disease and healthcare-associated infections (HAIs) are two distinct but significant health concerns that impact individuals and healthcare systems worldwide. In 2016, the European Centre for Disease Prevention and Control (ECDC) estimated that the burden of healthcare-associated pneumonia, surgical site infection, *Clostridioides difficile* infection, neonatal sepsis, urinary tract infection, and primary bloodstream infection, the six main types of HAI, was higher than the burden of 31 other infectious diseases combined.[1,2] Moreover, the majority of these infections are caused by multidrug-resistant organisms. It is well known that factors such as old water systems, inadequate, irrational, and prolonged usage of antibiotics, poor adherence to regulations regarding hand hygiene, disinfection, and sterilization processes are correlated with a higher incidence of HAIs, therefore surveillance systems were created to reduce mortality and morbidity associated with these type of infections.[3–6] There is a continuous fight against HAIs, as the burden of these infections is high and they represent a global public health issue.[1,7–9]

An important problem that needs to be highlighted is that low- and lower-middle-income countries, with limited medical resources, have a higher incidence of HAIs, resulting in a higher percentage of patients with disabilities and consequently increasing costs for their healthcare system. In these countries, information regarding HAIs and the burden of death caused by this type of infection are not as clear and complete as in high-income countries. Aside from the variations caused by objective factors, this issue makes it impossible to apply well-known characteristics regarding HAIs to other countries, regions, and hospitals from data that was already provided.[10–12]

Patients admitted to the intensive care unit (ICU) often undergo invasive procedures such as the insertion of urinary catheters, intravascular catheters, mechanical ventilation. Together with other risk factors, these procedures increase their susceptibility to developing HAIs,[1,2] which leads to prolonged hospitalization with a negative impact on both the patients and the healthcare system, more frequent readmissions, as well as an increase in morbidity and mortality.[3,4]

In order to reduce the incidence of HAIs and prevent the spread of antibiotic-resistant organisms, several organizations have recognized the importance of developing action plans to be implemented in hospitals all around the world.1 As antimicrobial resistance patterns vary greatly between countries and even hospitals, it is mandatory for each hospitals to take into consideration the local antimicrobial resistance patterns while establishing and implementing their action plans.[1]

Nowadays, antibiotic resistance is a multilateral problem, therefore it should be addressed from different perspectives. Developing new generations of antibiotics and conducting molecular epidemiological investigations represent necessary parts of a puzzle besides improving hygiene systems, safe disposal of medical waste, and following rigorous procedures for hand hygiene and sterilization processes, in order to reduce the rates of HAIs.[13–18]

Both cardiovascular disease and HAIs are multifaceted issues that require a comprehensive approach involving individuals, healthcare providers, public health organizations, and policymakers. Addressing these challenges can significantly improve patient outcomes and the overall effectiveness of healthcare systems.

The aim of this study is to evaluate the risk of death among patients with HAIs admitted to the ICU, hospitalized for cardiovascular diseases, compared to those with similar pathologies, without infections.

MATERIALS AND METHODS

STUDY DESIGN

A retrospective case–control study, including data from patients with cardiovascular diseases and HAIs versus patients with only cardiovascular diseases admitted to the ICU, was conducted in a tertiary public hospital from January 1, 2018 to December 31, 2021.

The inclusion criteria for the case group were chronic and acute cardiovascular diseases, such as valvular disease, ischemic coronary disease, aortic dissection, cardiac failure, acute myocardial infarction, and HAIs, and for the control group cardiovascular diseases without signs of infection. All patients were admitted to the ICU. The diagnosis of HAI was established after obtaining the results of body fluid culture and an epidemiological enquiry was conducted. Culture was performed for patients presenting systemic signs of infection, such as alterations in body temperature, changes in white blood cell count, tachycardia, tachypnea, or specific signs for each type of infection, such as skin infection (postoperative incision with inflammatory signs), gastrointestinal infection (diarrhea), urinary tract infection (dysuria, back tenderness), or pulmonary infection (productive cough, chest pain). Patients under 18 years of age were excluded from the study.

The study included 131 patients with cardiovascular diseases and infections with bacteria resistant to antibiotics and 131 patients with cardiovascular diseases and no signs

of infection. Patients from the control group were enrolled using systematic sampling based on ICU registers. All data collected were based on routinely collected hospital admission data. There was no interaction with patients, and information regarding laboratory findings was extracted from the informatics system used by healthcare providers in the hospital.

We performed a descriptive analysis of the patients' characteristics, multidrug-resistant (MDR) bacteria and outcomes of severe infection, as well as a case-control analysis in order to assess risk factors associated with death among patients with HAIs. Following the definitions for MDR, we evaluated carbapenems as a resistance marker for *Acinetobacter baumannii*, methicillin for *Staphylococcus aureus* (MRSA), vancomycin (VRE) for *Enterococcus spp.*, third generation cephalosporins and carbapenems for *Enterobacteriaceae*, and more than three antibiotic classes for *Pseudomonas aeruginosa*, including cephalosporins, floroquinolones, piperacillin-tazobactam, aminoglycosides, carbapenems, and colistin.[19]

ETHICS APPROVAL

The study was conducted in accordance with the Declaration of Helsinki and was approved by the ethical committee of the Cardiovascular Diseases and Transplant Emergency Institute of Târgu Mureş (no. 9920/14.12.2021). Written informed consent was obtained from all study participants.

STATISTICAL ANALYSIS

Statistical analysis was performed using the Statistical Package for Social Sciences (SPSS, version 23, Chicago, IL, USA). Data not found in charts or the informatics system were labeled as missing. Mean, median, and percentages were reported.

Risk factors that could be associated with death were analyzed using logistic regression and the multivariable model was created using a p value of <0.05, adjusting for all variables found significant in the univariable analysis and factors considered 'a priori', reporting crude odds ratio (OR), adjusted odds ratio (aOR), confidence intervals (CIs) (95%) and p values.

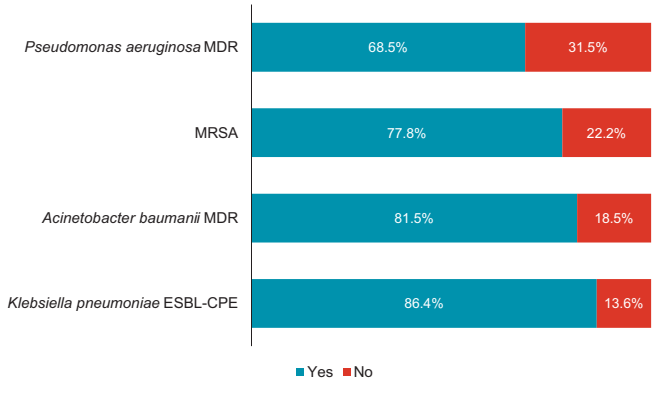

FIGURE 1. Multidrug resistance among the most frequent bacteria

RESULTS

CHARACTERISTICS OF THE STUDY GROUPS

A total of 262 patients were included, with a mean age of 62.61 years for the case group and 64.6 years for the control group. More than two thirds of patients were men (64.9% in the case group and 71% in the control group).

When evaluating the length of hospitalization in the ICU, there was a significant difference between the two groups (11 days in the case group vs. 2 days in the control group; p = 0.0001).

In the case group, the most frequent bacteria identified were *Klebsiella pneumoniae* (33.8%), followed by *Acinetobacter baumannii* (20.6%), *Staphylococcus aureus* (13.7%), *Pseudomonas aeruginosa* (11.5%), *Clostridioides difficile* (9.2%), and *Enterococcus faecalis* (4.6%). In 60.3% of cases, the infection was caused by a multidrug-resistant organism. From the 44 cases of infection caused by *Klebsiella pneumoniae*, 86.4% were *Enterobateriaceae* producing extended-spectrum beta-lactamases (ESBL) and carbapenemase (CPE), and from the 27 cases of infection caused by *Acinetobacter baumannii*, 81.5% were MDR (Figure 1).

In total, 60.3% of patients in the case group died, compared to 16.8% in the control group (p = 0.0001). From the 52 patients presenting an infection with a sensitive bacteria, 36.5% died and from the total of 79 patients with a multidrug resistant bacteria, 75.9% died (p = 0.0001).

In 75.9% of the patients who died, the infection was caused by a MDR bacterium, with a longer hospitalization in the ICU compared to those who survived (11 days vs. 2 days; p = 0.0001). *Klebsiella pneumoniae* was again the most frequent organism identified among patients who died (40.5%), the second most frequent being *Acinetobacter baumannii* (30.4%). The most common cardiovascular pathology among deceased patients was valvulopathy (34.2%), followed by chronic heart failure (30.4%) and acute myocardial infarction (30.4%).

TABLE 1. Uni- and multivariable analysis of risk factors associated with death among patients in the control group

Risk factors	Patients who survived n = 109	Patients who died n = 22	Univariable analysis		Multivariable analysis	
			cOR (95% CI)	p value	aOR (95% CI)	p value
Aortic dissection	8	3	1.93 (0.48–8.2)	0.33	–	–
Valvulopathy	46	1	1.21 (1.08–2.23)	0.04	1.12 (1.01–2.00)	0.04
Diabetes mellitus	8	2	1.26 (0.24–6.39)	0.77	–	–
Chronic hypertension	22	5	1.16 (0.38–3.49)	0.78	–	–
Ischemic cardiomyopathy	29	6	1.03 (0.36–2.89)	0.94	–	–
Cardiac failure	21	5	1.23 (0.4–3.72)	0.71	–	–
Acute myocardial infarction	7	9	10.08 (3.21–31.66)	0.001	5.39 (1.14–17.99)	0.04
Cardiorespiratory arrest	5	6	7.8 (2.12–28.57)	0.02	3.89 (0.95–15.92)	0.059

TABLE 2. Uni- and multivariable analysis of risk factors associated with death among patients in the case group

Risk factors	Patients who survived n = 52	Patients who died n = 79	Univariable analysis		Multivariable analysis	
			cOR (95% CI)	p value	aOR (95% CI)	p value
Aortic dissection	7	8	0.72 (0.24–2.13)	0.55	–	–
Valvulopathy	17	27	1.06 (0.5–2.24)	0.86	–	–
Diabetes mellitus	2	6	2.05 (0.39–10.59)	0.38	–	–
Chronic hypertension	16	20	0.76 (0.35–1.65)	0.49	–	–
Ischemic cardiomyopathy	4	18	3.54 (1.12–11.15)	0.03	3.49 (1.97–12.54)	0.04
Cardiac failure	12	24	1.45 (0.65–3.24)	0.36	–	–
Endocarditis	3	4	0.87 (0.18–4.06)	0.86	–	–
Acute myocardial infarction	8	24	2.4 (1.98–5.86)	0.04	2.41 (0.83–6.97)	0.10
Acute pulmonary edema	2	11	4.04 (1.85–19.05)	0.03	2.27 (0.41–12.43)	0.34
Cardiorespiratory arrest	7	17	1.76 (0.67–4.6)	0.24	–	–
Multidrug-resistant organism	19	60	5.48 (2.55–11.78)	0.0001	3.87 (1.53–9.18)	0.004
Klebsiella pneumoniae	12	32	2.26 (1.03– 4.98)	0.041	1.24 (0.46–3.36)	0.66
Acinetobacter baumannii	3	24	7.12 (2.02–25.13)	0.002	5.97 (1.53–23.28)	0.01
Pseudomonas aeruginosa	4	11	1.94 (0.58–6.46)	0.280	–	–
Staphylococcus aureus	8	10	0.79 (0.29–2.17)	0.658	–	–
Longer hospitalization in the ICU	–	–	–	–	1.03 (0.99–1.078)	0.11

Among patients in the control group, the most frequent cardiovascular disease was valvular disease (35.9%), followed by ischemic cardiomyopathy (26.7%) and hypertension (20.6%).

UNI- AND MULTIVARIABLE ANALYSES OF RISK FACTORS ASSOCIATED WITH DEATH

Patients from the control group who died were more likely to suffer from valvulopathy (OR: 1.21; 95% CI 1.08–2.23), acute myocardial infarction (OR 10.08; 95% CI 3.21–31.66) and previous cardiorespiratory arrest (OR 7.8; 95% CI 2.12–28.57), and after creating the multivariable model, valvulopathies were more likely to be associated with death in these patients (aOR 1.12; 95% CI 1.01–2.002) (Table 1).

When evaluating risk factors associated with death among patients with infections admitted to the ICU, acute myocardial infarction (OR 2.4; 95% CI 1.98–5.86) and acute pulmonary edema (OR: 4.04; 95% CI 1.85–10.05) were significant factors, and these patients were more likely to present an infection with *Klebsiella pneumoniae* (OR: 2.26; 95% CI 1.03–4.98) or *Acinetobacter baumannii* (OR: 7.12; 95% CI 2.02–25.13) (Table 2).

Acute myocardial infarction (OR: 4.72; 95% CI 2.4–9.27), cardiorespiratory arrest (OR: 3.66; 95% CI 1.73–7.74), acute pulmonary edema (OR: 4.79; 95% CI 1.48–15.50), infections with multidrug-resistant bacteria (OR: 10.93; 95% CI 5.87-20.37), *Klebsiella pneumoniae* (OR: 5.75; 95% CI 1.65-16.89), *Acinetobacter baumannii* (OR:16.41; 95% CI 4.79-56.2), and *Pseudomonas aeruginosa* (OR: 5.29;

TABLE 3. Uni- and multivariable analysis of risk factors associated with death among all patients in the study

Risk factors	Patients who survived n = 161 (61%)	Patients who died n = 101 (39%)	Univariable analysis		Multivariable analysis	
			cOR (95% CI)	p value	aOR (95% CI)	p value
Aortic dissection	15	11	1.19 (0.52–2.7)	0.67	–	–
Valvulopathy	63	28	1.59 (1.34–2.02)	0.04	0.68 (0.33–1.37)	0.28
Diabetes mellitus	10	8	1.29 (0.49–3.4)	0.59	–	–
Chronic hypertension	38	25	1.06 (0.59–1.9)	0.83	–	–
Ischemic cardiomyopathy	33	24	1.2 (0.66–2.19)	0.53	–	–
Cardiac failure	33	29	1.56 (0.87–2.78)	0.12	–	–
Endocarditis	3	4	2.17 (0.47–9.91)	0.31	–	–
Acute myocardial infarction	15	33	4.72 (2.4–9.27)	0.001	4.50 (1.92–10.51)	0.001
Acute pulmonary edema	4	11	4.79 (1.48–15.50)	0.009	1.13 (0.27–4.70)	0.85
Cardiorespiratory arrest	12	23	3.66 (1.73–7.74)	0.001	1.64 (0.61–4.44)	0.32
Multidrug-resistant organism	19	60	10.93 (5.87–20.37)	0.001	3.43 (1.31–8.95)	0.012
Klebsiella pneumoniae	12	32	5.75 (2.79–11.85)	0.001	2.01 (0.72–5.66)	0.18
Acinetobacter baumannii	3	24	16.41 (4.79–56.2)	0.001	8.99 (2.21–36.45)	0.002
Pseudomonas aeruginosa	4	12	5.29 (1.65–16.89)	0.005	3.63 (0.89–14.7)	0.07
Staphylococcus aureus	8	10	2.1 (0.8–5.51)	0.13	–	–
Being part of the case group	52	79	7.72 (4.22–13.39)	0.001	1.72 (0.07–3.97)	0.19

95% CI 1.65-16.89) were found to be statistically significant risk factors associated with death among all patients included in the study (Table 3). After adjusting for all variables found significant in the univariable analysis and prolonged hospitalization, a factor considered 'a priori', patients who died were more likely to present an infection with a multidrug-resistant bacteria (aOR: 3.43; 95% CI 1.31–8.95) or *Acinetobacter baumannii* (aOR: 8.99; 95% CI 2.21–36.45), and to present an acute myocardial infarction (aOR: 4.50; 95% CI 1.92–10.51) (Table 3).

DISCUSSION

The objective of this study was to highlight the risk of death among patients with cardiovascular emergencies admitted to ICUs in Romania, who acquire a HAI. HAIs are associated with a longer period of hospitalization and higher costs for the already affected Romanian healthcare system. The results of this study can help us see the importance of prevention and careful monitoring with measurable progress regarding the reduction of the rates of HAIs.

We identified a high rate of HAIs among patients admitted to ICUs caused by multiresistant germs (60.3%) compared to bacteria sensitive to antibiotic treatment (39.7%). The average age of patients in the case group was 62.61 years, similar to data reported in the study conducted by Voidazan *et al.*,[20] and 67.1% of these patients were men. Among the respective pathogens, Gram-negative bacteria had the highest frequency: *Klebsiella pneumoniae* (33.6%) and *Acinetobacter baumnannii* (20.6%). Similar results were obtained in a study conducted at a tertiary hospital in Jining, China, regarding the analysis of multiresistant bacteria.[21] In other studies, multidrug-resistant *Acinetobacter baumannii* was present in a significantly higher percentage of cases (43.48%) compared to our percentage of 20.6%, but *Klebsiella pneumoniae* was present in a lower percentage of cases (7.27%).[22] The number of deaths that occurred in patients with multiresistant infections was considerably higher compared to patients with infections sensitive to antibiotic therapy (75.9% vs. 22.4%). A higher probability of death was also observed in association with certain Gram-negative pathogens, such as *Klebsiella pneumoniae*, *Acinetobacter baumannii*, and *Pseudomonas aeruginosa*, an outcome also observed in studies on mortality associated with infections with multi-resistant Gram-negative germs and MRSA.[23,24] The probability of death was significantly higher in the case group, showing that infections are a major factor in patient prognosis. The alarming situation observed not only in this study but also in numerous other studies should put us in a heightened state of awareness, as we are at a critical moment in healthcare.[25–28]

The risk of death among patients admitted to the ICU is increased for patients presenting severe acute cardiovascular complications such as acute myocardial infarction, or severe chronic cardiovascular diseases like valvular

disease. For patients acquiring a HAI during their stay in the ICU, the risk of death is significantly higher than for those with similar cardiovascular pathologies, with a longer hospitalization and a consequent rise in costs for the healthcare system.

Intensive care units are the main frontline in the fight against infections because the vulnerability of patients is at its highest. Invasive monitoring devices, ventilators, and immunosuppression are some of the causes favoring the emergence of infections. In many cases, the biggest problem is represented by the limited treatment options. This is due to the ineffectiveness of antibiotic therapy caused by errors in prescribing the right antibiotic, dosage errors, low compliance in terms of doctor–patient collaboration, failure to observe the necessary time interval for treatment, and many others.

Regarding the length of hospitalization in the ICU, a longer hospitalization was associated with a significantly higher probability of death, illustrating the unfavorable prognosis related to the time required for treatment, similar to findings in other studies.[22] The longer the patient remains in the ICU, the higher the risk of acquiring an infection that can often become fatal. Acquiring a nosocomial infection also increases the length of hospitalization, which will lead to increased expenditure. Cost-effectiveness also benefits when the infection is treated correctly, and even more so when the infection is prevented. The occurrence of organ failure was also a decisive factor for the occurrence of death in the exploratory analysis performed on the 29 patients, the strongest statistical association being observed in the case of cardiovascular failure and respiratory failure. Similar results were observed in a study in which more days spent in the ICU were associated with higher long-term mortality in both ventilated and non-ventilated patients,[29] but another study resulted in a lack of association with risk of death in terms of ICU days.[30]

Studies have shown that inadequate antimicrobial treatment is an important risk factor for death in critical patients, suggesting that the aim should be to reduce the occurrence of this important problem by using efficient prophylactic methods.[31] Important studies have revealed the association of dysbiosis with the development of various pathologies including cardiovascular diseases, as the microbiota affects the host's immunity.[32]

Because of the steadily increasing incidence of nosocomial infections related to cardiac surgery in the last decades, prophylaxis should mainly target the prevention and appropriate treatment of bacteremia associated with invasive hospital-based procedures performed in high-risk patients. Further studies are needed in this area.

The limitations of our study include incomplete data from medical charts, a disadvantage created by retrospective collection of data, as well as the lack of information listed in our informatics system. The prospective extension of the study would enable us to collect all data needed, and information storage in our electronic system would facilitate data collection. Another limitation of our study is that we did not follow if the antibiotic treatment was changed after receiving the results of the culture and antibiogram, in order to establish the adequate use of antibiotics.

CONCLUSIONS

In conclusion, patients with cardiovascular diseases admitted to the ICU who acquired HAIs were more likely to die, in the majority of cases HAIs being caused by multiresistant germs. *Klebsiella pneumoniae*, *Acinetobacter baumannii*, and *Pseudomonas aeruginosa* were the organisms more likely to be involved in infections among patients who have died. It was shown that a higher probability of death is associated with a longer hospitalization, and one of the main causes for prolonged stay in the ICU was a nosocomial infection. Balancing the urgency of addressing cardiovascular emergencies with the need to prevent HAIs is a complex challenge. Healthcare providers must follow established protocols, maintain high standards of infection control, and collaborate across specialties to optimize patient outcomes in these critical situations.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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