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Cluster analysis identifies patients at risk of catheter-associated urinary tract infections in intensive care units: findings from the SPIN-UTI Network

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SUMMARY

Background: Although preventive strategies have been proposed against catheter-associated urinary tract infections (CAUTIs) in intensive care units (ICUs), more efforts are needed to control the incidence rate.

Aim: To distinguish patients according to their characteristics at ICU admission, and to identify clusters of patients at higher risk for CAUTIs.

Methods: A two-step cluster analysis was conducted on 9656 patients from the Italian Nosocomial Infections Surveillance in Intensive Care Units project.

Findings: Three clusters of patients were identified. Type of admission, patient origin and administration of antibiotics had the greatest weight on the clustering model. Cluster 1 comprised more patients with a medical type of ICU admission who came from the community. Cluster 2 comprised patients who were more likely to come from other wards/hospitals, and to report administration of antibiotics 48 h before or after ICU admission. Cluster 3 was similar to Cluster 2 but was characterized by a lower percentage of patients with administration of antibiotics 48 h before or after ICU admission. Patients in Clusters 1 and 2 had a longer duration of urinary catheterization [median 7 days, interquartile range (IQR) 12 days for Cluster 1; median 7 days, IQR 11 days for Cluster 2] than patients in Cluster 3 (median 6 days, IQR 8 days; $P<0.001$). Interestingly, patients in Cluster 1 had a higher incidence of CAUTIs (3.5 per 100 patients) compared with patients in the other two clusters (2.5 per 100 patients in both clusters; $P=0.033$).

Conclusion: To the authors' knowledge, this is the first study to use cluster analysis to identify patients at higher risk of CAUTIs who could gain greater benefit from preventive strategies.

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[1] Full details of the collaborators of the SPIN-UTI Network provided in Appendix section.

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Introduction

Healthcare-associated infections (HAIs) represent a pressing issue for public health, and one of the greatest challenges for healthcare professionals and policy makers. Although HAIs constitute a major threat in all healthcare settings [1], their incidence is higher in patients in intensive care units (ICUs) than in patients on other wards [2,3]. According to the European Centre for Disease Prevention and Control (ECDC), nearly 8% of patients admitted to an ICU for more than 2 days presented with at least one HAI on a given day [4,5]. Urinary tract infections (UTIs) are among the most common HAIs, representing up to 40% of all HAIs [6]. The presence of a urinary catheter and the duration of exposure – allowing continuous access of organisms into the urinary bladder – are the main risk factors for development of a catheter-associated UTI (CAUTI) [7]. Indeed, as reported by ECDC, the urinary catheter utilization rate was 78 per 100 patient-days in ICUs, and nearly 98% of UTIs were associated with the presence of a urinary catheter [6]. However, other host factors (i.e. anatomical or functional abnormalities, female sex, older age, diabetes mellitus, genetic predisposition), and bacterial (i.e. pathogen virulence characteristics) and healthcare (i.e. poor quality of catheter care, lack of antimicrobial therapy) characteristics may affect the risk of CAUTIs [8]. The burden of CAUTIs is associated with increased morbidity and mortality, longer length of stay and higher healthcare costs [9]. For instance, in the USA, it has been estimated that CAUTIs cause approximately US$131 million in annual excess medical costs [10]. In addition, urinary catheters are often reservoirs for multi-drug-resistant bacteria and a source of transmission to other patients [11]. CAUTIs are also associated with severe health outcomes including sepsis, a systemic inflammatory condition that occurs when bacteria infecting the urinary tract infect the bloodstream [9]. Surveillance data indicated that sepsis was associated with increased mortality and morbidity in patients of all ages [12,13]. Although preventive strategies, such as educational initiatives, catheter avoidance and limiting catheter days, have been proposed [14], more efforts are needed to control the incidence of CAUTIs and to improve patient outcomes. In fact, it has been estimated that up to 70% of CAUTIs may be preventable with recommended infection control measures [7,15–20].

In the era of precision medicine, identifying patients at risk of HAIs by coupling established clinicopathological features might be fundamental for developing novel preventive strategies tailored to each patient's requirements [21,22]. In 2005, the Italian Study Group of Hospital Hygiene of the Italian Society of Hygiene, Preventive Medicine and Public Health established the 'Italian Nosocomial Infections Surveillance in Intensive Care Units' (SPIN-UTI) project [13,23–28]. To date, the SPIN-UTI Network has surveyed approximately 20,000 patients, more than 4300 infections and 5300 micro-organisms. This study used cluster analysis to distinguish patients according to their characteristics at ICU admission, and to identify clusters of patients at higher risk for CAUTIs and associated sepsis. Accordingly, variability across clusters in terms of duration of urinary catheterization, and incidence of CAUTIs and associated sepsis was explored.

Methods

Study design and data collection

The ongoing SPIN-UTI project is being conducted in accordance with the protocol of the Hospitals in Europe Link for Infection Control through Surveillance (HELICS) Network, updated in accordance with the ECDC Healthcare-Associated Infections in Intensive Care Units protocol [29]. The current study was approved by the Ethics Committee of 'Catania 1', Catania, Italy (Protocol Nos. 111/2018/PO and 295/2019/EMPO), and details on study design and protocols have been described elsewhere [13,23–28,30]. In brief, hospital participation is voluntary and data are handled confidentially. Patients are included prospectively, and all data are collected for each patient staying in an ICU for more than 48 h. The SPIN-UTI project adopts a web-based data collection procedure by different electronic data forms using an online platform. In general, data regarding characteristics of hospitals and ICUs, patients, infections and associated micro-organisms are collected [23,24]. Since 2008, surveillance of ICU-acquired sepsis has been included in the SPIN-UTI protocol as severity of HAIs, using the definition of sepsis of the American College of Chest Physicians/Society of Critical Care Medicine Consensus Conference [31]. Therefore, the present study used data from the SPIN-UTI project conducted from 2008 to 2017. Patients staying in ICUs for more than 48 h with complete information on age, sex, Simplified Acute Physiology Score (SAPS) II score at admission, patient origin, type of admission, trauma, and administration of antibiotics within 48 h of admission were included in this study. According to standard case definitions reported in the HAI-ICU protocol, CAUTI was defined if an indwelling urinary catheter was in place within 7 days of a positive laboratory result for uropathogens (bacteria or fungi), or signs and symptoms meeting the criteria for UTI were evident [29].

Data processing

The original dataset was built by recording data related to ICU characteristics (type, percentage of mortality, proportion of intubated patients, proportion of patients with a urinary catheter), patient characteristics at admission (e.g. age, sex, SAPS II score, patient origin, admission type), dates of insertion and removal of invasive devices (e.g. urinary catheter), infection status (i.e. infection date, infection site, associated micro-organisms) and micro-organisms (i.e. antimicrobial resistance data). Next, the dataset was designed according to the 'not only Structured Query Language' (NoSQL) approach, useful for working with a wide variety of data models, including key value, document, columnar and graph formats. Common Python data analysis libraries, such as Pandas and Py-Mongo, were used in this study to process and analyse data. In particular, Py-Mongo contains tools for working with MongoDB, a NoSQL organized platform used to undertake traditional statistical analysis [32]. Finally, the online Plotly library was used for graphical data representation with a Sankey diagram.

Cluster analysis

Cluster analysis was conducted to group similar observations in a dataset, such that observations in the same cluster were similar to each other. In particular, the two-step clustering method was performed to identify different clusters of patients based on age, sex, SAPS II score at admission, patient origin, type of admission, trauma, and administration of antibiotics in 48 h before or after ICU admission [33]. The clustering algorithm, based on Schwarz's Bayesian Information Criterion (SBIC), allowed sets of clustered variables to be categorized. This algorithm is able to handle categorical and continuous variables, and to choose the exact number of clusters by comparing the values of a model-choice criterion across different clustering solutions. Furthermore, log-likelihood was chosen as a distance measure between individual data vectors [34]. Specifically, the optimal number of clusters was determined automatically according to the SBIC, a criterion for model selection based on the likelihood function [34]. Variables included in the cluster algorithm were ranked according to their predictive importance values, which ranged from 0.1 (i.e. low predictive ability) to 1 (i.e. high predictive ability) [34]. The cluster solution obtained was tested by excluding variables with predictive importance <0.2.

Visual analysis

A visual analytic approach inspired by the outflow graph visualization technique was also used. In general, this approach shows how different event pathways and patient records could lead to different outcomes. In this study, a Sankey diagram was used to visualize the flow of patients during their ICU stay, without temporal information. Sankey diagrams consist of nodes, the height of which represent patients in a particular 'state', while the height of each edge represents the number of patients that evolve into other 'states' [31].

Statistical analysis

Statistical analyses were performed using SPSS Version 22.0 (IBM Corp., Armonk, NY, USA). Descriptive statistics were used to characterize the population by median and interquartile range (IQR) or percentage. Kolmogorov–Smirnov test was used to assess the normal distribution of variables. In addition, Chi-squared test was used to analyse categorical variables, and Kruskal–Wallis *t*-test was used for continuous variables. All statistical tests were two-sided, and $P<0.05$ was considered to indicate statistical significance.

Results

Study population

Of 13,512 patients enrolled from 2008 to 2017, this study included 9656 SPIN-UTI participants admitted to 76 ICUs of 55 hospitals for a total of 101,417 patient-days. The remaining 3856 participants (28.5%) were excluded because data were missing for at least one variable imputed in the cluster analysis. In this subsample, 264 patients acquired at least one CAUTI, with a total of 271 CAUTIs; this resulted in a cumulative incidence of 2.7 CAUTIs per 100 patients (i.e. 264/9656) and an incidence density of 2.7 CAUTIs per 1000 patient-days (i.e. 271/101,417). Among the characteristics of patients at ICU admission, female sex ($P=0.033$), higher SAPS II score ($P<0.001$), medical type of ICU admission ($P<0.001$) and being a trauma patient ($P=0.011$) were positively associated with CAUTI acquisition.

Characteristics of clusters

Two-step cluster analysis was performed to distinguish different clusters of patients based on their characteristics at ICU admission. Across different clustering solutions, the best was characterized by three different clusters. Notably, the top three variables with higher predictive importance were administration of antibiotics in 48 h before or after ICU admission, type of ICU admission, and patient origin. These variables were followed by SAPS II score at admission, trauma, age and sex, which showed lower predictive importance. The exclusion of variables with predictive importance <0.2 (i.e. age and sex) did not significantly affect the cluster solution. Indeed, the majority of patients (98.5%) maintained the same cluster classification obtained by the whole model. Table I shows the characteristics of participants with relative within-cluster homogeneity and between-cluster variability in terms of age, sex, SAPS II score at admission, patient origin, type of admission, trauma, and administration of antibiotics in 48 h before or after ICU admission. In particular, Cluster 1 ($N=2143$) comprised more patients with a medical type of ICU admission who came from the community. This cluster was also characterized by an intermediate percentage of patients who received antibiotics in 48 h before or after ICU admission, higher proportion of trauma patients, lower median age and higher SAPS II score. Cluster 2 ($N=5854$) consisted of patients who were more likely to come from other wards/hospitals, and to report administration of antibiotics 48 h before or after ICU admission. This cluster included older patients with an intermediate SAPS II score, and approximately half of them reported a surgical type of ICU admission (i.e. 52.2%, the highest percentage across clusters). Patients in Cluster 3 ($N=1659$) were similar to those in Cluster 2 in terms of patient origin, type of admission and age. However, Cluster 3 was characterized by a lower percentage of patients with administration of antibiotics 48 h before or after ICU admission, and lower SAPS II score. No difference in terms of sex distribution across clusters was evident.

Duration of urinary catheterization

Overall, the duration of urinary catheterization was 85,799 days, which corresponded to an urinary catheter utilization rate of 84.6 urinary-catheter-days per 100 patient-days. Although length of ICU stay was similar across clusters, visual inspection of the Sankey diagram (Figure 1) revealed differences in terms of urinary catherization and its duration. In fact, participants belonging to Clusters 1 or 2 were less likely to be catheterized (82.9% and 84.1%, respectively) than patients in Cluster 3 (85.6%; $P<0.001$). However, patients in Clusters 1 or 2

Table I

Characteristics of clusters of patients at intensive care unit (ICU) admission and urinary catheter utilization.

Characteristics	Cluster 1 (*N*=2143)	Cluster 2 (*N*=5854)	Cluster 3 (*N*=1659)	*P*-value
Age, years	69 (24)	70 (20)	70 (20)	0.028
Sex (% men)	62.8%	61.0%	60.5%	0.263
Patient origin				
Other ward/healthcare facility	41.5%	87.3%	86.8%	<0.001
Community	58.5%	12.7%	13.2%	
SAPS II score at admission	40 (27)	38 (26)	37 (23)	<0.001
Type of ICU admission				
Medical	63.2%	47.8%	52.8%	<0.001
Surgical	36.8%	52.2%	47.2%	
Trauma	5.7%	4.4%	4.4%	0.043
Impaired immunity	5.8%	7.4%	3.6%	<0.001
Antibiotic treatment in 48 h before or after ICU admission	67.9%	87.0%	32.9%	<0.001
Length of ICU stay, days	5 (10)	5 (9)	4 (8)	0.134
Presence of urinary catheter during ICU stay	82.9%	84.1%	85.6%	<0.001
Duration of urinary catheterization, days	7 (12)	7 (11)	6 (8)	<0.001

SAPS II, Simplified Acute Physiology II.

Results are reported as median (interquartile range) for continuous variables, or percentage for categorical variables. Statistical analyses were performed using the Kruskal–Wallis or the Chi-squared test.

had a longer duration of urinary catheterization (median 7 days, IQR 12 days for Cluster 1; median 7 days, IQR 11 days for Cluster 2) compared with patients in Cluster 3 (median 6 days, IQR 8 days; *P*<0.001).

Incidence of CAUTIs and sepsis

In general, patients with urinary catheterization exhibited a higher incidence of UTIs than patients who were not catheterized (3.0 per 100 patients vs 1.2 per 100 patients; *P*=0.004). The rate of CAUTIs was 3.2 per 1000 catheter-days, with an incidence that increased with increasing duration of catheterization: 0.4 per 100 patients in those catheterized for <5 days, 0.8 per 100 patients in those catheterized for ≥5 days and ≤10 days, and 7.2 per 100 patients in those catheterized for >10 days (*P*<0.001). Interestingly, patients in Cluster 1 showed a higher incidence of CAUTIs (3.5 per 100 patients) than those in Clusters 2 or 3 (2.5 per 100 patients in both clusters; *P*=0.033).

Finally, this study found that 37.0% of patients with CAUTIs developed sepsis, but no difference was evident in the incidence of sepsis across clusters (*P*=0.238). However, the percentage of sepsis among patients with CAUTIs increased with increasing duration of catheterization: 30.0% in participants catheterized for <5 days, 35.0% in those catheterized for >5 days and <10 days, and 45.6% in those catheterized for >10 days (*P*=0.010).

Discussion

To the best of the authors' knowledge, this is the first study to use cluster analysis to identify patients at higher risk of CAUTIs according to their characteristics at ICU admission. This method meets the need to couple well-established clinicopathological features with the development of novel preventive strategies tailored to each patient's requirements [21,22]. In a subsample of 9656 SPIN-UTI patients, an incidence density of CAUTIs was reported that was similar to that reported by ECDC for European countries [6], and by the Centers for Disease Control and Prevention's National Healthcare Safety Network for the USA [35]. In this scenario, understanding modifiable and non-modifiable risk factors is crucial to

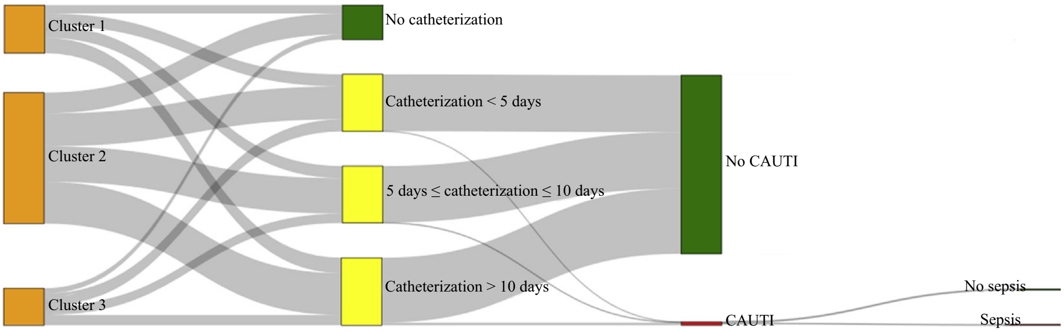

Figure 1. Outflow of patients during their stay in an intensive care unit. Sankey diagram describes the flow of patients from their admission to intensive care unit, urinary catheter utilization, and incidence of catheter urinary tract infections and sepsis. CAUTI, catheter-associated urinary tract infection.

control the incidence of CAUTIs and prevent adverse outcomes. Several host characteristics may affect the risk of CAUTIs [8]. In general, women have a higher risk of UTIs than men, probably due to the short distance from the urethra to the rectum [36,37]. Other risk factors for CAUTIs include increasing age, non-surgical disease hospitalization and diabetes mellitus [20,38]. The present findings support that female sex, severity (i.e. higher SAPS II score), medical type of ICU admission, and being a trauma patient were positively associated with CAUTIs. However, non-adherence to aseptic catheter care recommendations should be considered as this has been associated with increased risk of bacteriuria [14,20,38].

With respect to urinary catheterization, in agreement with previous reports [39], this study found that the urinary catheter utilization rate was 84.6 urinary-catheter-days per 100 patient-days. In agreement with the general consensus, this study found that urinary catheterization and its duration are the main risk factors for UTIs and CAUTIs [17,18,38]. Catheters induce an immune response with accumulation of fibrinogen on the surface. This event leads to an ideal environment for the attachment of uropathogens, which multiply, form biofilms, promote epithelial damage and can seed infection of the kidneys [40]. Indeed, in this study, patients with urinary catheterization exhibited higher incidence of UTIs, while the incidence of CAUTIs increased with increasing duration of catheterization.

Next, three clusters of patients were identified based on their characteristics at ICU admission. Notably, patient origin, type of admission, and administration of antibiotics in 48 h before or after ICU admission were the top three predictors that characterized each cluster; however, there were slight but significant differences in age, SAPS II score at admission and proportion of trauma patients. While Cluster 1 mainly consisted of patients with a medical type of ICU admission who came from the community, the other two clusters were mainly characterized by patients who came from other wards or hospitals and with various types of ICU admission. However, the proportion of patients who received antibiotics 48 h before or after ICU admission was higher in Cluster 3. Interestingly, differences were observed between clusters in terms of urinary catherization and duration [14,17,18,38]. Patients in Cluster 1 showed a higher incidence of CAUTIs than patients in Clusters 2 and 3. If untreated, uropathogens can cross the tubular epithelial cell barrier and cause sepsis [40], a critical condition associated with increased mortality [41]. This study found that 37.0% of patients with CAUTIs had sepsis, and this percentage increased with increasing duration of catheterization. However, no difference was found in the incidence of sepsis across clusters.

Although several patient characteristics are commonly considered as risk factors for CAUTIs (e.g. age, sex, type of hospitalization, clinical history, severity), no previous studies have used a clustering approach to simultaneously assess the incidence of CAUTIs among different groups of patients. To the best of the authors' knowledge, only the study by Yelin *et al.* has proposed a machine learning algorithm to predict the risk of antibiotic resistance in UTIs, based on demographic and clinical history of patients [42]. Thus, the present findings, together with those from other studies, could be helpful for the prevention of CAUTIs in the near future, which has become a priority for public health. Indeed, the identification of a cluster at higher risk of CAUTIs could indicate which patients might gain greater benefit from preventive strategies. Several infection control measures have been proposed to reduce the incidence of CAUTIs [7,15—20], most of which rely on educational initiatives towards catheter avoidance, aseptic technique during catheterization, and limiting catheter use. In addition, alternatives to indwelling urinary catheters have been considered, such as condom catheters or intermittent catheterization [16].

In a broader context of personalized prevention and medicine against infections, combining patient's characteristics and drug history data could guide future preventive interventions tailored to specific subgroups of patients at highest risk, substantially improving the current standard of care [43]. Even more interestingly, the application of genome sequencing to pathogens and the combination of pathogen factors (i.e. genotypic and phenotypic) with clinical data could lead to the development of predictive models helpful in the management of infectious diseases [44]. However, we are still at the very beginning of the personalized medicine era, especially for the management of communicable diseases, and more efforts are needed to overcome limitations of current research and bring benefits in clinical practice [44].

Some aspects of the study findings should be interpreted with caution. Although three clusters of patients with high within-cluster homogeneity and between-cluster variability were identified, interpretation was not immediate. These clusters varied widely in terms of patient origin, type of ICU admission and antibiotic administration, with minor differences in age and severity, and no difference in sex distribution. Interestingly, patients who mainly came from the community with a medical type of ICU admission were at highest risk of CAUTIs, probably due to their prolonged urinary catheterization. However, other characteristics — including those that differed slightly between clusters — may affect these findings. As such, research should further decipher what factors collected at ICU admission might characterize different patient groups, and which mainly contribute to the risk of CAUTIs.

Despite these considerations, this study is the first to use a clustering approach to identify a subgroup of patients at higher risk of CAUTIs according to their characteristics at ICU admission. In the authors' opinion, this cluster of patients could gain greater benefit from personalized preventive strategies due to their longer urinary catheterization and higher incidence of CAUTIs. However, further studies are needed to confirm these findings and to develop preventive strategies tailored to personal and clinical characteristics of patients admitted to ICUs.

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Appendix

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Conflict of interest statement

None declared.

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