Comparative Mortality Analysis in Febrile and Afebrile Emergency Department Patients with Positive Blood Cultures: A Retrospective Study

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Abstract: This retrospective analysis at a major Italian university hospital (January 2018–September 2022) assessed the prognostic significance of fever in patients with bloodstream infections (BSIs). Of the 1299 patients with positive blood cultures, a comparison between febrile and afebrile patients at emergency department admission was conducted. This study particularly focused on the mortality rates associated with these two groups. Notably, afebrile patients exhibited a higher mortality rate. The odds ratio for mortality in afebrile patients was significantly higher compared to febrile patients. This suggests that the absence of fever might be an indicator of increased mortality risk, highlighting the complexity of diagnosing bloodstream infections based on fever presence. This study contributes to the understanding of fever as a diagnostic marker in emergency settings.

Keywords: fever; bloodstream infection; emergency department; mortality; prognostic indicator

1. Introduction

Bloodstream infections represent a significant public health challenge globally, characterized by their severe clinical implications and high mortality rates. The epidemiology of BSIs is complex, with varying prevalence rates reported across different regions and healthcare settings. The prevalence of bloodstream infections can vary significantly, with higher rates observed in hospital settings compared to the community [1]. The pathogens responsible for these infections are diverse, ranging from common bacteria like *Staphylococcus aureus* to more resistant strains such as methicillin-resistant *Staphylococcus aureus* (MRSA), with the latter posing significant treatment challenges [2]. The mortality rate associated with BSIs remains high, despite advances in medical care, underscoring the urgency for improved diagnostic and therapeutic strategies [3]. The impact of these infections is not limited to morbidity and mortality; they also place a significant economic burden on healthcare systems due to prolonged hospital stays and the need for complex treatments.

Timely identification and treatment of infections, particularly bloodstream infections, are crucial for patient outcomes. This is especially true in the context of sepsis and septic shock, where early recognition and prompt antibiotic administration are well-established determinants of survival [4,5]. However, timely recognition of systemic infection is paramount to prevent progression to sepsis. On the other hand, the clinical presentation of infections can be insidiously subtle, especially in certain patient populations such as the elderly, the immunocompromised, or those with multiple comorbidities, posing...
significant challenges to healthcare providers. Atypical presentation of sepsis has been correlated with poorer outcomes [6].

The population’s demographic shift towards an older age spectrum, combined with the increasing prevalence of complex chronic health conditions, has led to a rise in atypical presentations of infections in the emergency department (ED).

The interplay between comorbid conditions like diabetes, chronic kidney disease (CKD), and immunosuppression and bloodstream infections is complex and significantly affects both the clinical presentation and prognosis of these infections.

In patients with diabetes, the immune system’s compromised state often exacerbates the severity of infections. The hyperglycemic environment can impair neutrophil function, reduce phagocytosis, and weaken the overall antimicrobial response [7]. This impaired immune response increases the susceptibility to severe infections and can result in atypical presentations, which often delays diagnosis and treatment.

Chronic kidney disease (CKD) presents another layer of complexity. Patients with CKD experience alterations in immune function, including impaired leukocyte activity and decreased response to vaccinations, rendering them more susceptible to infections [8].

For individuals who are immunosuppressed, either due to HIV/AIDS or as a result of immunosuppressive therapies, the risk of bloodstream infections is markedly increased. The lack of an adequate immune response in these patients not only predisposes them to a higher prevalence of infections but also leads to atypical, often severe presentations [9]. Furthermore, these infections in immunosuppressed patients are often caused by opportunistic or uncommon pathogens, complicating diagnosis and treatment strategies.

This shift necessitates a re-evaluation of traditional diagnostic markers, particularly the role of fever, in infection diagnosis. While fever is a hallmark sign of infection and a key component in sepsis criteria, its absence should not be overlooked, as it may mask the presence of a serious underlying condition.

These comorbidities highlight the need for heightened clinical awareness and tailored management strategies in patients with bloodstream infections. Early recognition, appropriate antimicrobial therapy, and comprehensive management of the underlying comorbidities are crucial for improving outcomes in these vulnerable populations.

Several studies have suggested that the absence of fever in patients with sepsis and septic shock may be associated with poorer outcomes, potentially both due to delayed diagnosis and treatment and to the lack of the beneficial physiological effects of increased body temperature [10]. Moreover, clinical trials have reported no benefit of body temperature control on clinically relevant outcomes in septic patients [10]. This underscores the need for heightened clinical vigilance and a more nuanced understanding of infection presentations in the ED. However, the prognostic implications of fever (or absence thereof), to our knowledge, have seldom been studied in patients not fulfilling the criteria for sepsis and septic shock and not admitted to the Intensive Care Unit (ICU). The prognostic implication of the absence of fever at the initial presentation in the ED has rarely been studied, to our knowledge, in patients with bloodstream infection, with or without sepsis. Furthermore, fever has typically been analyzed solely as an objective indicator during hospitalization, in the ICU, or throughout the emergency department (ED) visit. Its role as a historical or anamnestic symptom has not been previously explored. Specifically, there is a possibility that patients presenting without fever at the ED might have experienced fever or chills earlier. Our study seeks to contribute to the existing literature by examining the prognostic significance of having or not having a fever at the time of ED admission in patients with bloodstream infections.

In this retrospective analysis, we examine the correlation between reported or measured fever at initial presentation and in the preceding week and mortality outcomes in patients with positive blood cultures in the emergency department, also considering how these characteristics are distributed in various age groups and what correlation they present with the degree of patients’ comorbidity.
2. Materials and Methods

2.1. Study Design

This study employed a retrospective design, utilizing a comprehensive review of emergency department charts. The objective was to assess the prognostic significance of fever, or its absence, in relation to survival outcomes in patients with bloodstream infections identified upon admission to the emergency department.

Our research was conducted at a large university hospital, comprising over 1000 beds and catering to both medical and surgical specialties. This facility also serves as a major trauma referral center in a densely populated metropolitan area in Italy.

The study period was from January 2018 to September 2022. A total of 3640 cases were evaluated, and a total of 1299 cases were submitted for analysis.

We systematically gathered all positive blood culture results from patients aged 18 or older who were admitted to our emergency department over four years. Inclusion criteria were as follows: only patients whose blood cultures were obtained during their stay in the emergency department within the first 12 h of admission and who were subsequently hospitalized (not discharged from the ED or transferred to another healthcare facility) were considered. The patients’ ED electronic health records were reviewed to extract relevant data, including sex, age at admission, species of the isolated microorganism, comorbidities, the presence or absence of fever during the initial ED assessment (both at triage and during the first evaluation by an ED physician), and the antibiotic resistance pattern of the isolated microorganism.

Patients were considered to have fever at the initial evaluation, both at the triage or the first evaluation by the treating physician, if any of the following was reported: fever, increased body temperature, chills, unexplained night sweats, or if a body temperature of 37.0 °C or higher was reported in the seven days preceding the ED admission. When the anamnestic record was ambiguous, this was resolved by collegial review by all the authors; if, after a collegial review, no conclusion had been reached, the datum was considered missing.

Microorganisms which exhibited resistance to more than two classes of antibiotics were considered multi-resistant [11].

The comorbidities were extracted from the ED record and were used to calculate the Charlson comorbidity index [10]. For patients for whom the initial evaluation in the ED electronic record was considered unsatisfactory, the comorbidities were not extracted, and the Charlson comorbidity index was considered missing for the purpose of the final analysis.

Moreover, the outcome of the hospital admission was collected from the hospital’s central database. When the outcome of the admission was not available, the case was not included in the final analysis.

When more than a single set of blood cultures were ordered in the same ED admission, the patient was considered to have a single microorganism if all samples yielded the same result and to have a polymicrobial infection if more than a single microorganism was isolated.

Since, in our ED, discharged patients may be recalled for admission if a blood culture becomes positive, when a single patient had two ED admissions, no further than a week apart, of which one resulted in discharge and one in hospital admission, those two different ED admissions were consolidated into one.

2.2. Statistical Analysis

We categorized the age and Charlson score into three distinct groups, transforming these into ordinal categorical variables. Specifically, patients with a Charlson score of 0 to 2 were categorized as having a low Charlson score, those with scores from 3 to 4 as medium, and those scoring 5 or above as high [10]. Age was similarly categorized: patients under 65 years old were considered young, those between 65 and 84 years old as middle-aged, and patients 85 years or older as old. Discharge status was treated as a binary categorical
variable (either discharged or deceased), and the presence of fever and multi-resistant microorganism were each considered dichotomous categorical variables.

Patients were stratified into two groups based on the presence or absence of fever, and their mortality rates were compared using a two-tailed test for proportions for independent samples. Further stratification was performed according to their age group, Charlson score, and the presence of multi-resistant bacteria, with a comparative mortality analysis for each subgroup carried out in the same manner.

Finally, a logit regression analysis was conducted to evaluate the independent contribution of each variable, including Charlson score category (low, medium, high), age group (young, middle-aged, old), presence or absence of multi-resistant bacteria, and presence or absence of fever to in-hospital mortality.

Data analysis was performed using the R language for Statistical Computing, version 4.3.2 [12], using the Tidyverse dialect v1.0 [13] and via the RStudio Desktop IDE v2024.04.1+748.pro2 [14] (2024 Posit Software, PBC formerly RStudio, PBC). Relative risks and confidence intervals for RR were calculated with the epiR package v 2.0.75 [15].

3. Results

During the specified timeframe, there were 1299 admissions with at least one set of positive blood cultures. Of these, 720 were male (55.4%). Triage and admission evaluations provided sufficient data to calculate a Charlson score for all patients.

3.1. Patient Demographics and Clinical Characteristics

In our cohort, 220 blood cultures were from patients with a Charlson score below 3 (16.9%), 369 had a score of 3 or 4 (28.4%), and 710 had a score of 5 or higher (54.7%). Age distribution was as follows: 428 blood cultures were from patients below 65 years old (32.9%), 689 were from patients aged between 65 and 84 (53.0%), and 182 were from patients aged 85 or older (14.0%).

The analysis revealed that the median age of patients was 70 years, with a standard deviation of ±15 years. When comparing febrile (N = 1073) and afebrile (N = 226) patients, the median ages were 69 and 71 years, respectively, with no statistically significant difference (p = 0.32) (Table 1).

<table>
<thead>
<tr>
<th>Age</th>
<th>All Cases N 1299</th>
<th>Fever N 1073</th>
<th>No Fever N 226</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>65–84 years</td>
<td>689 (53%)</td>
<td>984 (53.5%)</td>
<td>305 (35.3%)</td>
<td>0.98</td>
</tr>
<tr>
<td>≥85 years</td>
<td>182 (14%)</td>
<td>242 (13.2%)</td>
<td>83 (14.6%)</td>
<td></td>
</tr>
<tr>
<td>&lt;65 years</td>
<td>428 (32.9%)</td>
<td>613 (33.3%)</td>
<td>182 (31.9%)</td>
<td></td>
</tr>
<tr>
<td>Sex (Male)</td>
<td>720 (55.4%)</td>
<td>599 (55.8%)</td>
<td>121 (53.5%)</td>
<td>0.53</td>
</tr>
<tr>
<td>Charlson Comorbidity Index</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0–2</td>
<td>220 (16.9%)</td>
<td>185 (18.1%)</td>
<td>35 (12.7%)</td>
<td>0.04</td>
</tr>
<tr>
<td>3–4</td>
<td>369 (28.4%)</td>
<td>296 (28.9%)</td>
<td>73 (19.8%)</td>
<td></td>
</tr>
<tr>
<td>5+</td>
<td>710 (54.7%)</td>
<td>543 (53.0%)</td>
<td>167 (60.7%)</td>
<td></td>
</tr>
<tr>
<td>Triage code</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>200 (15.4%)</td>
<td>139 (13%)</td>
<td>61 (27%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>2</td>
<td>585 (45%)</td>
<td>480 (44.7%)</td>
<td>105 (46.5%)</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>226 (17.4%)</td>
<td>203 (18.9%)</td>
<td>23 (10.2%)</td>
<td>&gt;0.001</td>
</tr>
<tr>
<td>4</td>
<td>284 (21.9%)</td>
<td>248 (23.1%)</td>
<td>36 (15.9%)</td>
<td></td>
</tr>
<tr>
<td>Death</td>
<td>259 (19.9%)</td>
<td>187 (17.4%)</td>
<td>72 (31.9%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Multi-resistant strain</td>
<td>505 (38.9%)</td>
<td>427 (39.8%)</td>
<td>78 (34.5%)</td>
<td>0.14</td>
</tr>
<tr>
<td>Fungal</td>
<td>39 (3%)</td>
<td>37 (3.4%)</td>
<td>2 (0.9%)</td>
<td>0.04</td>
</tr>
</tbody>
</table>
3.2. Mortality Analysis

Mortality varied significantly across Charlson score groups and age groups. Among the 428 patients under 65, 70 died during hospitalization (16.4%); among the 689 patients aged 65 to 84, 123 died (17.8%); and among the 182 patients aged 85 or above, 66 died (36.3%). Examining mortality rates by Charlson score revealed that among the 220 patients with a score below 3, 12 died (5.5%); among the 369 with a score between 3 and 4, 31 died (8.4%); and among the 710 with a score of 5 or above, 216 died (30.4%). The differences in mortality between both age groups and Charlson score groups were statistically significant ($p < 0.001$ for both) (Figure 1).

Figure 1. Mortality according to the presence or absence of fever.

Comparing patients with and without fever at presentation, those without fever showed a higher mortality rate. Of the 226 patients who did not present with fever, 72 died (31.9%), whereas among the 1073 patients with fever at presentation, 187 died (17.4%), yielding a relative risk of death twice as high in patients without fever at presentation (RR 2.23, 95% CI 1.60–3.11, $p < 0.001$).

This difference in mortality persisted even after adjusting for the Charlson score, age group, and presence of a multi-resistant microorganism. Multivariate analysis revealed that the absence of fever was strongly associated with overall mortality. Specifically, the odds ratio for mortality in patients without fever at presentation was 2.23 (95% CI 1.60–3.11, $p < 0.001$). Additionally, the odds ratio for mortality in patients aged 85 and above compared to those below 65 was 2.11 (95% CI 1.31–3.41, $p = 0.01$), and for those with Charlson scores of 5 or above compared to those with scores below 3 it was 3.35 (95% CI 1.86–6.40, $p < 0.001$) (Table 2) (Figure 2).
Table 2. Odds ratios for mortality with reference to the variables of interest.

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Odds Ratio</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Absence of fever</td>
<td>2.23 [1.60–3.11]</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Age group</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>65–84 years</td>
<td>1.33 [0.91–1.99]</td>
<td>0.15</td>
</tr>
<tr>
<td>≥85 years</td>
<td>2.11 [1.31–3.41]</td>
<td>0.01</td>
</tr>
<tr>
<td><strong>Charlson range</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3–4</td>
<td>2.01 [1.10–3.87]</td>
<td>0.03</td>
</tr>
<tr>
<td>≥5</td>
<td>3.35 [1.86–6.40]</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Microbiology findings</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Multi-resistant</td>
<td>1.37 [1.03–1.83]</td>
<td>0.03</td>
</tr>
</tbody>
</table>

3.3. Triage Code Analysis

Analysis of triage codes indicated significant differences in the severity of presentation between febrile and afebrile patients. Patients were assigned triage codes from 1 (most urgent) to 4 (least urgent). Among afebrile patients, there was a higher percentage of triage code 1 (27%) compared to febrile patients (13%), indicating a more severe initial presentation (p < 0.001). Conversely, febrile patients were more likely to have triage codes 2 and 3 compared to afebrile patients.

3.4. Length of Stay

The length of stay (LOS) in the hospital did not significantly differ between febrile and afebrile patients, with median LOS being 16 days for febrile patients and 17 days for afebrile patients (p = 0.86). This suggests that the presence or absence of fever at presentation does not substantially affect the duration of hospitalization.
3.5. Multi-resistant Strains

Regarding the presence of multi-resistant strains, 505 patients (38.9%) had infections caused by multi-resistant organisms. The distribution was similar between febrile (39.8%) and afebrile (34.5%) patients, and this difference was not statistically significant ($p = 0.14$). However, the presence of multi-resistant strains was associated with increased mortality, with an odds ratio of 1.37 (95% CI 1.03–1.83, $p = 0.03$).

3.6. Microorganism Analysis

The five most frequently encountered microorganisms were Escherichia coli, Staphylococcus aureus complex, polymicrobial infections, Klebsiella pneumoniae, and Enterococcus faecalis. Escherichia coli was the most common, accounting for 30.41% of the cases, followed by polymicrobial infections at 14.63%, and Staphylococcus aureus complex at 13.32%.

4. Discussion

Infections are a common problem in emergency department patients, and bloodstream infections pose a particular concern. In this retrospective study, we showed that the absence of fever is associated with poorer outcomes. Specifically, mortality was doubled for patients without fever compared with those with fever. This association remained strong even after correcting for age, comorbidities, and the presence or absence of a multi-resistant microorganism. The absence of fever showed an increase in odds ratio comparable to that of advanced age and the second largest increase in odds ratio.

There are several possible explanations for this finding. First, from an evolutionary point of view, it is a highly conserved mechanism both in cold- and warm-blooded species and has been proposed to be a beneficial physiological response to infections [16]. Proposed underlying mechanisms include an increase in activity of both cellular and humoral immune responses and an increase in activity of circulating cytokines [16,17] and increased susceptibility of bacteria to antimicrobial drugs and molecules [17].

Secondly, fever may alert the physician that an infectious process is taking place, and febrile patients may receive antibiotic therapy sooner than afebrile patients [6,15,18]; indeed, physician awareness to sepsis has been linked to more aggressive treatment [15,19].

Third, afebrile patients may be frailer, have significant comorbidities, or have an impaired inflammatory response; on the other hand, absence of fever may be a consequence of more severe disease. Indeed, hypothermic patients with sepsis have been found to have a higher mortality and a higher rate of complications in a study in the ICU setting [18]. Fever is a key component of immune response; on the other hand, immune response has significant metabolic costs. Murine experimental models suggest that there is a trade-off between the metabolic requirements of immune response and the metabolic requirements of homeostasis; according to this model, increased homeostatic requirements may lead the organism to shift immune response toward a higher degree of pathogen tolerance [18]. Thus, it is possible to speculate that lack of fever may be a sign of reduced metabolic capabilities or reduced nutritional reserves. In contrast with this idea, Ito and colleagues have shown an interaction between body temperature and body mass index, whereas hypothermia is not associated with increased mortality in septic patients with either low or high BMI, while the association is present in patients with normal BMI [20]. Moreover, the association of hypothermia and mortality has been reported to be blunted, or even absent, in elderly patients, compared with non-elderly patients with sepsis admitted to ICU [20,21]. This is partially in contrast with our results, as the association between absence of fever and mortality remained after correcting for advanced age. This may be due to several reasons, including the different patients’ population (sepsis patients admitted to ICU versus patients with any type of bloodstream infection), the different definition of fever (we did not collect data about the actual temperature nor the temperature trajectory during hospital stay but only about the presence or absence of fever at presentation), or other unmeasured confounders. Our results are more in keeping with a large study on temperature trajectories in patients with any type of infection, whereas patients without
fever at admission were more likely to die in hospital than those with fever [22]. Notably, in this study the association between lack of fever and mortality persisted in elderly patients who were, also, more likely to be hypothermic. It is important to point out that most of the referenced studies focused on patients with sepsis, where fever was evaluated solely as an objective clinical sign, rather than as a historical or anamnestic symptom. To our knowledge, few studies have addressed the relationship between fever and mortality in ED patients regardless of sepsis and septic shock. Yamamoto and colleagues, for example, showed a marked decrease in mortality for patients with any type of infection who were febrile during the ED evaluation, compared with those who were afebrile or had mild hypothermia, with an adjusted odds ratio which ranged from 0.2 to 0.1, according to the temperature range [4].

Dias and colleagues reported an earlier initiation of antibiotic therapy in febrile ICU patients with sepsis or septic shock compared to afebrile patients, while, on the other hand, finding that timing of antibiotic administration only partially explained an observed difference in mortality [13]. In their study, there was a 5-fold increase in mortality for afebrile patients compared to febrile ones. Several other studies conducted in the ICU and ED setting on patients with sepsis and septic shock have reached similar conclusions [11,12,14], while fewer studies have addressed the question in the general ED population (i.e., with or without septic shock).

Hypothermia is a well-known response to infection, and it is part of the definition of sepsis. In our study, we could not distinguish between normothermia and hypothermia, as we relied on anamnestic records. However, a bimodal response to infection has been recently described in a large patients’ sample, with a majority of patients showing a hyperthermic response to infection and a minority showing hypothermia [21]. Notably, in this study, hypothermic and normothermic patients showed increased mortality. In keeping with this observed bimodal distribution of temperature, fever is a well-known component of attempts at distinguishing sepsis phenotypes [22].

To our knowledge, this is the first study to focus specifically on patients with bloodstream infection during the emergency department evaluation and to also include anamnestic record of fever in the week preceding the ED admission. The strengths of our study include the large sample size, the reliance on blood culture results to define bloodstream infection, and the availability of antibiotic resistance patterns of isolated microorganisms.

Our study has several limitations that should be kept in mind by the reader. First, it is retrospective in nature and based on the review of ED records. Thus, the quality of available data may impact the quality of the results. Indeed, for a large proportion of patients, it was not possible to calculate the Charlson comorbidity index due to poor anamnestic records. Secondly, we did not distinguish between false-positive blood cultures due to contaminant bacteria and true-positive blood cultures; however, coagulase-negative staphylococci and bacteria, which are commonly considered contaminants, were rare in our sample; moreover, we analyzed only patients admitted to the hospital who can be considered to have a clinical picture of sufficient severity to warrant admission.

We also did not distinguish between patients with sepsis or septic shock and those with infection but without sepsis, and we did not collect data about the timing and appropriateness of antibiotic therapy, which could have helped explain the association between lack of fever and mortality.

Moreover, we did not collect data on laboratory examinations, which could have provided valuable insight about the inflammatory response of the patients.

Finally, we relied on anamnestic records and on measurement of vital parameters during the initial evaluation to define the presence or absence of fever. On one hand, this could have led us to misclassify febrile patients based on incomplete clinical records; on the other hand, this has allowed us to consider febrile patients who displayed fever or associated symptoms in the days preceding the ED evaluation.
5. Conclusions

Our study on the association between the absence of fever and increased mortality in patients with bloodstream infections in the emergency department setting has revealed several critical insights with profound clinical implications. The finding that afebrile patients exhibit a higher mortality rate challenges conventional diagnostic approaches and underscores the need for heightened vigilance and a broader perspective when evaluating patients who might be harboring serious infections.

The traditional reliance on fever as a primary indicator of infection needs to be re-evaluated. This study suggests that the absence of fever, often overlooked or underestimated in clinical settings, may in fact be an indicator of a more severe health status.

Furthermore, our research highlights the importance of comprehensive patient assessment in the emergency department. Medical practitioners should be encouraged to consider a wide range of symptoms and signs, beyond the presence of fever, to improve the detection and treatment of bloodstream infections. This approach could lead to earlier and more effective interventions, potentially improving patient outcomes.

The study also opens avenues for further research. Future studies could focus on developing more sensitive diagnostic tools and strategies to identify at-risk afebrile patients. Additionally, investigating the underlying mechanisms that contribute to the absence of fever in severe infections could provide valuable insights into patient management and treatment strategies.

In conclusion, the findings of this study serve as a reminder of the complexities of diagnosing and managing bloodstream infections in the emergency department. They underscore the need for a more nuanced and comprehensive approach to patient care, one that recognizes the limitations of traditional markers like fever and embraces a more holistic view of patient symptoms and indicators.

Author Contributions: All authors provided substantial intellectual contribution to this article. Specifically, the roles are as follows: conceptualization, N.B., D.A.D.P., R.M. and M.C.; data curation, D.A.D.P., T.D., B.F., A.C., A.P. and M.P.; formal analysis, N.B. and D.A.D.P.; methodology, N.B., D.A.D.P. and R.M.; project administration, F.F. and M.C.; resources, T.D., B.F. and A.S.; supervision, A.G., F.F. and M.C.; validation, R.M.; writing—original draft, N.B., D.A.D.P. and M.F.; writing—review and editing, M.F., A.G., and F.F. All authors have read and agreed to the published version of the manuscript.

Funding: This research received no external funding.

Institutional Review Board Statement: This study was conducted in accordance with the Declaration of Helsinki and approved by the Ethics Committee of IRCCS Fondazione Policlinico Universitario Agostino Gemelli of Rome.

Informed Consent Statement: Being a retrospective study performed on a database of anonymized patients, informed consent was not required.

Data Availability Statement: The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

Conflicts of Interest: The authors declare no conflicts of interest.

References


