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Septic source matters: how infection site and microbial etiology affect sepsis prognosis

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Abstract

Sepsis is a life-threatening organ dysfunction caused by a dysregulated host response to infection. Despite advances in critical care, mortality remains high. This study assesses the relationship between septic source, microbial etiology, and in-hospital mortality. This prospective observational study was conducted at the St. Anna University Hospital of Ferrara, Italy, from October 2021 to February 2022. Adult patients with suspected sepsis and a qSOFA score ≥ 2 were included. Data collected included vital signs, laboratory values, septic source classification, microbial etiology, and in-hospital mortality. Statistical analyses were performed using SPSS and jamovi, with an alluvial diagram to visualize relationships. Of 200 screened patients, 187 were included (mean age 85.0±9.6 years). In-hospital mortality was 27.3%. The most common septic sources were urinary (43.3%) and respiratory (28.9%), followed by miscellaneous (11.8%), abdominal (7.0%), and undefined (9.1%). Undefined sources had the highest mortality (58.8%), followed by respiratory (31.5%) and urinary sepsis (22.2%) (p=0.002). Microbial etiology varied by source, with negative cultures (50.3%) being the most common result. No direct association between microbial etiology and mortality was found (p=0.470), but mortality differed when analyzed in conjunction with septic source. The alluvial diagram highlighted complex interactions between infection site, microbial etiology, and survival demonstrating that the septic source significantly impacts in-hospital mortality (p=0.012). Septic source significantly impacts in-hospital mortality, with undefined

infections carrying the highest risk. The interplay between microbial etiology and infection site influences outcomes. Early infection source identification and tailored antimicrobial strategies are crucial for improving sepsis management.

Background

Sepsis is a life-threatening organ dysfunction caused by a dysregulated host response to infection.[1] It represents a major global health burden, with millions of cases reported annually and high mortality rates despite advances in critical care management.[2,3] The latest guidelines emphasize the importance of early recognition and timely intervention, as delays in diagnosis and treatment significantly increase the risk of adverse outcomes.[4]

Sepsis is one of the leading causes of death worldwide, with an estimated 49 million cases and 11 million sepsis-related deaths per year.[2,5] The incidence of sepsis continues to rise due to an aging population, increased antibiotic resistance, and the growing prevalence of immunosuppressed patients.[6] In high-income countries, mortality has gradually declined due to improved critical care protocols and early sepsis detection programs,[7,8] but in low- and middle-income countries, sepsis remains a leading cause of in-hospital mortality.[5] The combined hospital mortality rate for sepsis and septic shock varies between 20% and 50%, depending on severity, comorbidities, and treatment efficacy.[6-8] Furthermore, despite growing awareness and improved management strategies, the identification of high-risk patients remains challenging.[4,9] The source of infection and microbial etiology have been increasingly recognized as crucial determinants of sepsis outcomes.[10,11]

Respiratory tract infections, particularly pneumonia, are among the most common causes of sepsis and are associated with high mortality rates. Urinary tract infections, on the other hand, are generally linked to better survival outcomes. Abdominal sepsis, though less frequent, challenges significantly physicians due to the need for early source control. Patients in whom the infection source remains undefined often have worse outcomes, possibly due to delays in diagnosis and treatment.[10-12] Understanding these factors is essential for optimizing antimicrobial therapy, guiding infection control measures, and improving patient prognosis.[4,9-12]

The microbiological etiology of sepsis further influences clinical outcomes. Gram-Negative (GN) bacteria, such as *Escherichia coli* and *Klebsiella pneumoniae*, are frequently implicated in urinary and abdominal sepsis, whereas Gram-Positive (GP) pathogens like Staphylococcus aureus and Streptococcus pneumoniae are common in respiratory infections. Culture-Negative (NC) sepsis remains a major challenge, occurring in up to 40–60% of cases, often due to prior antibiotic exposure or difficulties in pathogen isolation. Fungal Infections (FI), particularly Candida species,

are less common but associated with poor prognosis, especially in critically ill and immunocompromised patients.[11]

Given the importance of septic source and microbial etiology in determining sepsis outcomes, this study aimed at assessing their relationship with In-Hospital Mortality (IHM). Specifically, we sought to: i) evaluate the impact of different infection sources on patient survival; ii) investigate the distribution of microbial etiologies across septic sources; and iii) determine whether microbial etiology influences mortality when stratified by septic source. Our findings provide insight into the complex interactions between infection site, microbial profile, and clinical outcomes in septic patients, with potential implications for risk stratification and therapeutic strategies.

Materials and Methods

This is a single-center, prospective observational study conducted at the S. Anna University Hospital of Ferrara, Italy. The recruitment period spanned from October 2021 to February 2022. The study was approved by the local Ethics Committee (protocol n. 447/2021/Disp/AOUFe), and written informed consent was obtained from all enrolled patients or their relatives in cases of severe clinical conditions. Patients were eligible for inclusion if they met the following criteria: i) age ≥ 18 years; ii) clinical suspicion of an infectious disease; iii) quick Sequential Organ Failure Assessment (qSOFA) score ≥ 2. Patients who were subsequently determined not to have sepsis were excluded from the final analysis. Given that the study protocol was designed prior to the publication of the 2021 sepsis guidelines, the qSOFA score was used as the screening tool for sepsis severity. The following clinical and laboratory parameters were collected for each patient i) vital signs and laboratory values necessary to calculate the Sequential Organ Failure Assessment (SOFA) score; ii) sepsis source classification, categorized as respiratory, urinary, abdominal, miscellaneous, or undefined; iii) microbiological etiology, classified as NC, GP, GN, or FI; iv) final diagnosis; and v) IHM. The septic source was classified as “undefined” when no clear site of infection could be identified at the end of the ED diagnostic workup, despite microbiological sampling and bedside or radiological investigations. All collected data were recorded in a standardized database for subsequent statistical analysis.

In the ED, all non-shocked patients received empirical antibiotic therapy based on local epidemiology and institutional protocols within 3 hours from the first medical evaluation. In patients presenting with septic shock, empirical antibiotic therapy was initiated within 1 hour from ED assessment.

Statistical analysis

Continuous variables were summarized as mean ± Standard Deviation (SD) while categorical variables were reported as absolute frequencies and percentages. The chi-square test (χ^2) was used to assess associations between categorical variables, including the relationship between septic source, microbial etiology, and IHM. In cases where expected frequencies were low, Fisher's exact test was applied. To evaluate the interaction between septic source and microbial etiology on mortality, stratified analyses were performed.

A Sankey (alluvial) diagram was generated to visually represent the relationships between microbial etiology, septic source, and IHM. This diagram illustrates the proportional distribution of each variable, allowing for an intuitive visualization of patient flow across categories. Given the constraints in displaying directly numerical values within the figure, detailed data were reported in contingency tables.

A p-value < 0.05 was considered statistically significant. All analyses were conducted using SPSS Statistics (IBM Corp., Armonk, NY, USA) and Jamovi Project (Version 2.3-2025, available on https://www.jamovi.org) for graphical representations.

Results

An initial cohort of 200 patients was screened for analysis. Of these, 13 patients were determined not to have sepsis and were therefore excluded, resulting in a final study population of 187 eligible patients with a mean age of 85.0 ± 9.6 years. The IHM rate was 27.3% (n=51), while 72.7% (n=136) of patients survived. Septic shock was observed in 10 patients (5.3% of the study population). Vasopressor support was initiated in 6 cases, while in the remaining patients' escalation was withheld due to advanced age and severe comorbidities, as it was deemed unlikely to modify clinical outcome.

The primary septic sources were urinary (43.3%), respiratory (28.9%), miscellaneous (11.8%), abdominal (7.0%), and undefined (9.1%). A statistically significant association was observed between septic source and in-hospital mortality (p=0.002). Among non-survivors, the most frequent septic sources were urinary (35.3%) and respiratory (33.3%), followed by undefined (19.6%), miscellaneous (9.8%), and abdominal (2.0%). The highest mortality rate was recorded in patients with an undefined septic source (58.8%), followed by respiratory sepsis (31.5%), urinary sepsis (22.2%), miscellaneous (22.7%), and abdominal sepsis (7.7%) (Table 1).

Microbial etiology varied across septic sources (Table 2). The majority of patients had NC (50.3%), followed by GN bacterial infections (28.3%), GP bacterial infections (17.6%), and FI (3.7%). Respiratory sepsis was predominantly associated with NC (64.8%), followed by GP (18.5%) and GN (14.8%). Urinary sepsis had the highest proportion of GN pathogens (45.7%), followed by NC

(39.5%). Abdominal sepsis was most commonly linked to NC (61.5%), with an equal proportion of GP and GN (15.4% each). Miscellaneous infections had the highest percentage of GP pathogens (36.4%) and the lowest proportion of NC pathogens (40.9%). Undefined septic sources were primarily due to NC pathogens (58.8%), followed by GP (29.4%) and GN (11.8%).

Analysis of the relationship between microbial etiology, septic source, and IHM showed no statistically significant direct association (p=0.470) (Table 3). However, mortality varied depending on both the pathogen type and infection site. Among NC infections, mortality ranged from 12.5% in abdominal sepsis to 50.0% in undefined sources. In GP infections, mortality was 30.0% for respiratory sepsis, 0% for abdominal sepsis, and 60.0% for undefined septic sources. In GN infections, mortality was 0% for abdominal sources, 18.9% for urinary sepsis, 37.5% for respiratory sepsis, and 100% for undefined septic sources.

The alluvial diagram (Figure 1) illustrates the relationship between microbial etiology, septic source, and in-hospital mortality, demonstrating that the septic source significantly impacts IHM (p=0.012).

Discussion

In this study we found a significant association between septic source and IHM, with the highest mortality observed in undefined and respiratory sepsis. Additionally, microbial etiology varied significantly by septic source, but its direct association with mortality was not significant. However, stratified analysis revealed that GN infections in undefined sources had a particularly high mortality rate. Although disease severity and early management variables are known to influence sepsis outcomes, our findings suggest that septic source is associated with distinct mortality patterns already at the ED stage, supporting its role as an early prognostic phenotype rather than a mere surrogate of advanced disease severity.

Our findings are consistent with previous studies that highlight the prognostic significance of septic source in sepsis-related mortality. Respiratory sepsis has been frequently associated with worse outcomes compared to urinary and abdominal infections. A large retrospective cohort study by Vincent et al. found that respiratory infections had a significantly higher mortality rate compared to other infection sites,[13] which aligns with our results showing 31.5% mortality rate in respiratory sepsis. Similarly, a meta-analysis demonstrated that septic patients with an undefined source had increased mortality, likely due to diagnostic delays and suboptimal initial management.[14] Our data support these findings, emphasizing the importance of early and accurate source identification. The high mortality observed in patients with an undefined septic source should not be interpreted as a diagnostic failure, rather as the expression of an early and particularly vulnerable sepsis phenotype.

In these patients, the absence of a clearly identifiable source during the initial ED assessment may reflect atypical presentations, delayed radiological findings, or intrinsic diagnostic limitations in very elderly subjects. All these aspects may contribute to worse outcomes.

Negative Cultures (NC) were the most prevalent in respiratory infections (64.8%), consistent with prior literature. A previous study suggested that up to 60% of pneumonia-related sepsis cases remain culture-negative, often due to prior antibiotic exposure or non-bacterial pathogens.[15] Our findings further confirm this trend, highlighting the challenge of pathogen identification in pulmonary infections. In contrast, urinary sepsis in our cohort was most frequently associated with GN bacteria (45.7%), which aligns with reports indicating that Escherichia coli and Klebsiella spp. are the most common urinary pathogens in septic patients.[16-19]

The role of microbial etiology in sepsis mortality remains debated. Some studies have reported higher mortality in GN compared to GP infections due to more severe inflammatory responses and higher resistance rates.[20-23] However, others have found no significant difference in mortality between GN and GP infections. Our study provides additional insights by showing that mortality associated with microbial etiology is highly dependent on the septic source. Notably, the 100% mortality rate in GN infections with an undefined source raises significant concerns, as it suggests that these patients may be particularly vulnerable due to late diagnosis and inadequate early treatment. This is in line with findings from an ICU-based study, which demonstrated that septic patients with unidentified sources and GN bacteremia had the highest mortality risk.[24,25]

Fungal Infections (FI) were relatively rare in our cohort (3.7%), but their association with high mortality is consistent with prior research. The 100% mortality rate observed in respiratory FI mirrors previous reports indicating that pulmonary candidiasis and invasive aspergillosis in septic patients are associated with extremely poor outcomes.[26] These results underscore the importance of a high clinical vigilance and prompt antifungal treatment in high-risk patients.

Although antimicrobial resistance was not specifically analyzed in this study, it may have contributed to adverse outcomes in some subgroups, particularly in GN and FI, and should be explored in future specifically designed studies to address resistance-related prognostic factors.

The findings of this study have several implications. First, the high mortality associated with undefined septic sources underscores the importance of early and accurate source identification.[27] Rapid diagnostic tools, such as next-generation sequencing and point-of-care molecular assays, may help reduce the number of undefined infections and improve early therapeutic decisions.[28] Second, the interaction between microbial etiology and septic source suggests that antimicrobial therapy should be tailored not only to pathogen susceptibility but also to the presumed location of infection.[29,30] In particular, patients with GN infections and undefined septic sources may require

more aggressive management strategies, including broader initial antimicrobial treatment and early consideration of adjunctive therapies, such as extracorporeal blood purification techniques.[31] Furthermore, our results highlight the need for enhanced antimicrobial stewardship programs, particularly in patients with culture-negative sepsis.[29] The high prevalence of NC infections, especially in respiratory sepsis, suggests that empirical antibiotic selection should be optimized to balance effective coverage with antimicrobial resistance concerns.[18-23,29] The alluvial diagram used in our analysis provides an intuitive visualization of these relationships and could be employed in clinical settings to aid decision-making strategies.

In our cohort, 50.3% of patients had NC, a finding consistent with previous literature reporting that 40–60% of sepsis cases remain culture-negative.[32,33] This phenomenon is often attributed to prior antibiotic exposure, difficulties in pathogen isolation, or infections caused by non-bacterial organisms. NC sepsis was predominant in respiratory infections, mirroring data from pneumonia-related sepsis studies where a significant proportion of cases lack microbiological confirmation.[34] These findings highlight the challenge of pathogen identification in sepsis management and emphasize the need for improved diagnostic techniques, such as molecular and metagenomic approaches, to reduce the burden of undefined infections and optimize antimicrobial therapy.

An important feature of our study population was the high proportion of elderly patients with a mean age significantly above the general sepsis population and most of them were institutionalized or required permanent medical devices. Advanced age is a well-established risk factor for sepsis-related mortality, given the presence of multiple comorbidities, immunosenescence, and the increased likelihood of multidrug-resistant infections. Moreover, institutionalized patients frequently harbor long-term indwelling devices (e.g., urinary catheters, feeding tubes, and tracheostomies), which act as potential entry points for infections, particularly GN and fungal pathogens.[35,36] Although the advanced age of our cohort may limit the generalizability of these findings to younger populations, it reflects the growing burden of sepsis among very elderly patients presenting to the ED. In this setting, frailty, immunosenescence, and long-term device dependence may amplify the prognostic impact of septic source.

This analysis has different strengths. First, its prospective design, which allowed for comprehensive data collection on septic source, microbiology, and outcomes. Additionally, the use of an alluvial diagram provided a novel and effective method to illustrate the interplay between septic source, microbial etiology, and mortality. This visualization technique is particularly useful for understanding complex relationships that may not be immediately apparent from traditional statistical analyses.

On the other hand, our study has limitations. First, as a single-center study, our findings may not be generalizable to other institutions with different patient populations or antimicrobial resistance patterns. Second, the reliance on qSOFA as a screening tool (due to the study's design before the release of the 2021 sepsis guidelines) may have influenced patient selection compared to studies using NEWS-2 criteria.[37] Third, the high prevalence of NC infections, while consistent with previous reports, raises the possibility that prior antibiotic use or suboptimal culture techniques may have influenced microbiological findings. Further studies incorporating advanced microbiological diagnostics, such as metagenomic sequencing, may help address this issue. Due to the limited sample size and the small number of patients in several etiological and source-specific subgroups, multivariable modelling and formal interaction testing were not performed to avoid overfitting and unreliable estimates.

Future research should focus on larger, multicenter cohorts to improve external validity. Additionally, studies evaluating the impact of rapid diagnostic technologies on reducing the proportion of undefined infections could help refine sepsis management strategies. Given the striking mortality differences observed in GN infections based on septic source, further investigation into the host-pathogen interactions driving these outcomes is warranted. Finally, integrating machine learning models with clinical and microbiological data may provide personalized risk stratification tools to guide sepsis treatment more effectively.

Conclusion

Our study demonstrated that septic source is a key determinant of IHM, with undefined infections carrying the highest risk. While microbial etiology alone is not a strong predictor of mortality, its impact varies significantly by infection site, with GN infections in undefined sources exhibiting very poor outcomes. These findings emphasize the importance of early source identification, tailored antimicrobial therapy, and improved diagnostic strategies to optimize sepsis management and reduce mortality. Future studies should aim to refine risk prediction models and explore novel therapeutic interventions to improve outcomes in high-risk septic patients.

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Table 1. Association between septic source and in-hospital mortality. The highest mortality percentage is observed in undefined septic sources (19.6%) (p= 0.002).

Septic Source	**Survived n=136 (n, %)**	**Deceased n=51 (n, %)**	**Total n=187 (n, %)**
Respiratory	37 (27.2)	17 (33.3)	54 (28.9)
Urinary	63 (46.3)	18 (35.3)	81(43.3)
Abdominal	12 (8.8)	1 (2.0)	13 (7.0)

Miscellaneous	17 (12.5)	5 (9.8)	22 (11.8)
Undefined	7 (5.1)	10 (19.6)	17 (9.1)

IHM: In-hospital mortality; FI: Fungal infection; GN: Gram negative; GP: Gram positive; NC: Negative culture.

Table 2. Distribution of microbiological etiologies by septic source.

Septic Source	**NC n=94 (n, %)**	**GP n=33 (n,%)**	**GN n=53 (n, %)**	**FI n=7 (n, %)**	**Total n=187 (n, %)**
Respiratory	35 (64.8)	10 (18.5)	8 (14.8)	1 (1.9)	54 (28.9)
Urinary	32 (39.5)	8 (9.9)	37 (45.7)	4 (4.9)	81 (43.3)
Abdominal	8 (61.5)	2 (15.4)	2 (15.4)	1 (7.7)	13 (6.9)
Miscellaneous	9 (40.9)	8 (36.4)	4 (18.2)	1 (4.5)	22 (11,8)
Undefined	10 (58.8)	5 (29.4)	2 (11.8)	0 (0.0)	17 (9,1)

FI: Fungal infection; GN: Gram negative; GP: Gram positive; NC: Negative culture.

Table 3. Relationship between microbiological etiologies, septic source, and in-hospital mortality. The χ^2 resulted 3.55 (p= 0.470).

Etiology	**Total (n, %)**	**Septic Source**	**Survived (n, %)**	**Deceased (n, %)**
NC	94 (50.3)	*Respiratory*	25 (71.4)	10 (28.6)
		Urinary	24 (75.0)	8 (25.0)
		Abdominal	7 (87.5)	1 (12.5)
		Miscellaneous	6 (66.7)	3 (33.3)

		Undefined	5 (50.0)	5 (50.0)
GP	33 (17.6)	*Respiratory*	7 (70.0)	3 (30.0)
		Urinary	6 (75.0)	2 (25.0)
		Abdominal	2 (100.0)	0 (0.0)
		Miscellaneous	5 (62.5)	3 (37.5)
		Undefined	2 (40.0)	3 (60.0)
GN	53 (28.3)	*Respiratory*	5 (62.5)	3 (37.5)
		Urinary	31 (83.8)	6 (16.2)
		Abdominal	1 (50.0)	1 (50.0)
		Miscellaneous	3 (75.0)	1 (25.0)
		Undefined	0 (0.0)	2 (100.0)

IHM: in-hospital mortality; GN: Gram negative; GP: Gram positive; NC: Negative culture.

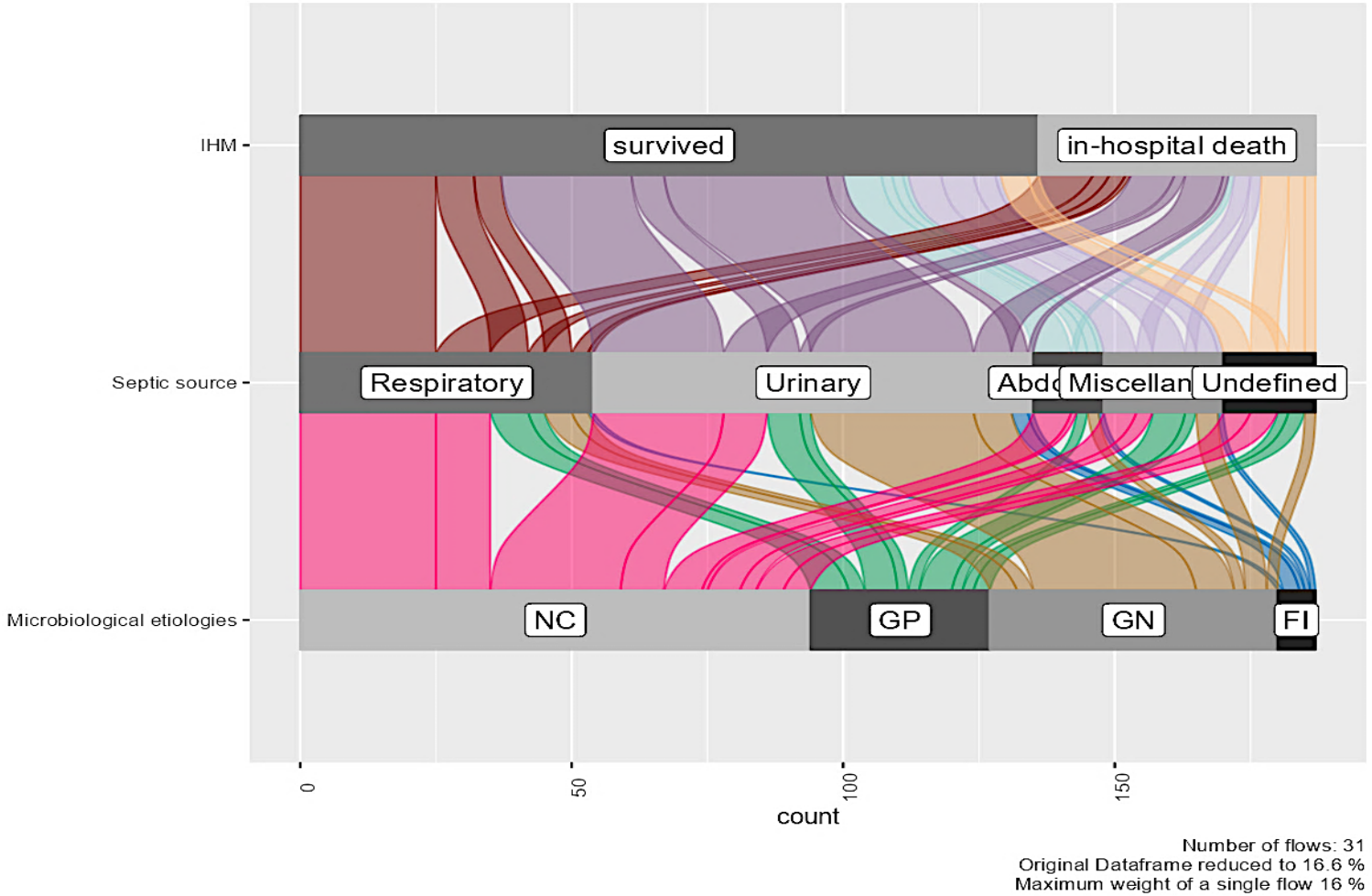


Figure 1. Alluvial diagram illustrating the relationship between microbial etiology, septic source, and in-hospital mortality. Each flow represents the proportional distribution of patients across microbial categories, infection sources, and survival status. The width of each stream is proportional to the number of patients in each subgroup, allowing visualization of how septic source and microbial etiology jointly relate to in-hospital mortality. The

septic source significantly impacts in-hospital mortality (p= 0.012). FI: Fungal infection; GN: Gram negative; GP: Gram positive; NC: Negative culture.

Contributions: Conceptualization: M.G.; Data analysis: M.G., and M.D.S.; Methodology: M.G., A.C., M.M., C.C., R.D.G. and M.D.S.; Project administration: M.G. and R.D.G.; Supervision: M.G., C.C. and R.D.G.; Writing original draft: M.G.; Writing/review & editing: M.G., G.M., F.L., C.D., C.B., C.C. and R.D.G. All authors have read and agreed to the published version of the manuscript.

Conflict of interest: the authors declare no potential conflict of interest, and all authors confirm accuracy.

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