Journal of Intensive Medicine 5 (2025) 64–69

Contents lists available at ScienceDirect

Journal of Intensive Medicine

journal homepage: www.elsevier.com/locate/jointm

Original Article

Previous treatment with anthracycline does not affect the course of sepsis in cancer patients: Retrospective cohort study

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ARTICLE INFO

Managing Editor: Jingling Bao/Zhiyu Wang

Keywords:
Cancer
Sepsis
ICU
Anthracycline
Vasopressor

ABSTRACT

Background: Cancer patients who are exposed to sepsis and had previous chemotherapy may have increased severity. Among chemotherapeutic agents, anthracyclines have been associated with cardiac toxicity. Like other chemotherapeutic agents, they may cause endothelial toxicity. The aim of this study was to evaluate the effect of anthracycline treatment on the outcome of cancer patients with sepsis.

Methods: Data from cancer patients admitted to intensive care units (ICUs) for sepsis or septic shock were extracted from the Groupe de Recherche Respiratoire en Réanimation Onco-Hématologique database (1994–2015). Comparison between patients who received anthracycline and those who did not was performed using a propensity score, including confounding variables (age and underlying diseases). A competing risk adjusted for severity of illness (Sequential Organ Failure Assessment [SOFA] score) was used to analyze the duration of vasopressor requirement.

Results: Among 2046 patients, 1070 (52.3%) patients who received anthracycline were compared with 976 (47.7%) who did not. The underlying disease was mostly acute hematological malignancy (49.2%). Sepsis, mostly pneumonia (47.7%), had developed 2 days (interquartile range [IQR]:1–4 days) prior to ICU admission. Most patients (n=1156/1980,58.4%) required vasopressors for 3 days (IQR: 2–6 days). Factors associated with the need for vasopressors were aplasia (hazard ratio [HR]=1.72, 95% confidence interval [CI]: 1.21 to 2.47, P=0.002) and day 1 respiratory SOFA score (HR=7.07, 95% CI: 2.75 to 22.1, P <0.001). Previous anthracycline treatment was not associated with an increased risk of vasopressor use. The duration of vasopressors was not different between patients who received anthracycline and those who did not (P=0.79). Anthracycline was not associated with ICU mortality.

Conclusion: Previous anthracycline treatment did not alter the course of sepsis in a cohort of cancer patients admitted to intensive care with sepsis.

Introduction

Although anthracyclines remain an important chemotherapy drug for the treatment of several cancers (particularly breast cancer and hematological malignancies), they are associated with a high risk of cardiotoxicity. Anthracyclines have been associated with cumulative, dose-dependent cardiac toxicity related to several mechanisms. The first mechanism includes the

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https://doi.org/10.1016/j.jointm.2024.07.005
Received 9 April 2024; Received in revised form 15 July 2024; Accepted 25 July 2024
Available online 24 September 2024

interaction between topoisomerase 2 and DNA, leading to cardiomyocyte death. Other mechanisms include nitric oxide release, mitochondrial damage, and iron accumulation, leading to oxidative stress associated with sarcomere dysfunction and an inflammatory state associated with cell death.[1,2] Acute cardiac toxicity (<1%), which is transient and manifests as impaired contractile function, remains rare. The incidence of chronic heart failure varies according to the drug, cumulative dose, and age of the patient, but it can reach 7%–26% in patients treated with doxorubicin at 550 mg/m^2 and as high as 18%–48% at 700 mg/m^2.[3] Heart failure can be uni- or biventricular dysfunction with impaired contractile function and loss of cardiomyocytes, leading to loss of left ventricular wall thickness and dilatation of the ventricular cavity. The consequences are reduced contractility, reduced posterior wall thickness, increased ventricular afterload, and diastolic dysfunction, leading to irreversible dilated heart disease. Although sometimes asymptomatic, heart failure can also be associated with various complications. In particular, in the context of sepsis, chronic heart failure could be more severe and has been associated with more severe shock. However, immunosuppressed patients with cancer have more than a ten fold higher risk of sepsis than the general population, with some variability depending on the type of cancer.[4,5] In fact, sepsis remains the most common reason for intensive care unit (ICU) admission in cancer patients[6] and is associated with higher morbidity and mortality rates and longer hospital stays. The aim of the study was to evaluate the effect of anthracycline treatment on the course of patients with septic cancer.

Methods

Patients and study design

The Groupe de Recherche Respiratoire en Réanimation Onco-Hématologique (GRRR-OH) database includes data on all cancer patients admitted to the seven ICUs between 1994 and 2015 and included in one of the 14 prospective or retrospective studies published by the research group (https://www.grrroh.fr/).

The primary objective was to compare the course of sepsis between patients who had previously received anthracyclines and those who had not.

Data collection

Data on cancer patients admitted to the ICU with sepsis were extracted from this database.[7–19] This study was a secondary analysis of the GRRR-OH sepsis database. The relevant institutional review board (IRB) approved each study.[9,17,20–30] In this secondary analysis of the sepsis database, only patients without missing data on previous anthracycline treatment were included. Sepsis was defined according to the Third International Conference on Sepsis Definition (Sepsis-3).[31] Multiple organ failure was defined as the association of three organ dysfunctions specified by the need for organ support (vasopressors, mechanical ventilation, and renal replacement therapy [RRT]). Invasive management during ICU such as mechanical ventilation, vasopressors needs, and RRT were analyzed. Aplasia at ICU admission was defined as grade 4 neutropenia with a neutrophil count <500/mm^3. Comorbidities included peripheral vascular disease, cirrhosis, chronic kidney disease, diabetes mellitus, congestive heart failure, chronic obstructive pulmonary disease, and dementia. The Sequential Organ Failure Assessment (SOFA) score was calculated on admission as previously defined.[9,32–34] The adjusted SOFA score was defined as the SOFA score without the hemodynamic component.

All studies included in the merged database were approved by the IRB or local ethics committee according to French law at the time of the study (Supplementary Table S1).

Statistical analysis

Outcome measures included the need for vasopressors, ICU mortality, and duration of vasopressor infusion. All data were expressed as *n* (%) or median (interquartile range [IQR]) as appropriate. In case of missing data, percentage was calculated on the real number of data, but statistical analysis included missing data.

To assess the effect of prior anthracycline treatment on vasopressor use and mortality, a multivariate analysis was performed, including characteristics on the first day of ICU admission and factors associated with anthracycline use.

Although patients who received anthracycline are different from patients who did not receive it, the propensity score (PS) for receiving anthracycline was used to adjust for confounding factors. First, a directed acyclic graph was performed with variables considered by the authors to be confounding or collider bias to receive anthracyclines (age as well as underlying diseases such as solid tumor, acute hematological disease, and chronic hematological disease). Second, we calculated the PS using logistic regression based on these characteristics with a 1:1 matching algorithm without replacement, a caliper of 0.2. The matched population was then used for logistic regression, including the variables considered confounding factors of sepsis severity to assess the impact of anthracycline (adapted SOFA score without hemodynamic score, vasopressor need, comorbidity, aplasia, duration of symptoms before ICU admission). Third, a competing risk analysis (including end of vasopressor treatment or death) was performed to compare vasopressor infusion duration between patients with and without prior anthracycline treatment using the PS-based population. Patients without data on vasopressor duration were excluded from this analysis.

All analyses were performed with R software version 3.6.2 (The R Foundation for Statistical Computing). The packages “TableOne,” “Survival,” “Survminer,” “Comprsk,” and “matchIt” were used to perform the analyses. Missing data were not imputed.

Results

Baseline characteristics

As described in the flowchart, 2062 patients were included in the database, including 16 patients with missing data on previous anthracycline treatment (Figure 1). In the remaining 2046 patients, the median age was 59 (range: 48–67) years, and 1031 out of 1903 (54.2%) patients had at least one comorbidity (including cardiac, pulmonary, or renal comorbidity as described in the Charlson Comorbidity Index). The underlying diseases were acute hematological diseases (*n*=1007,

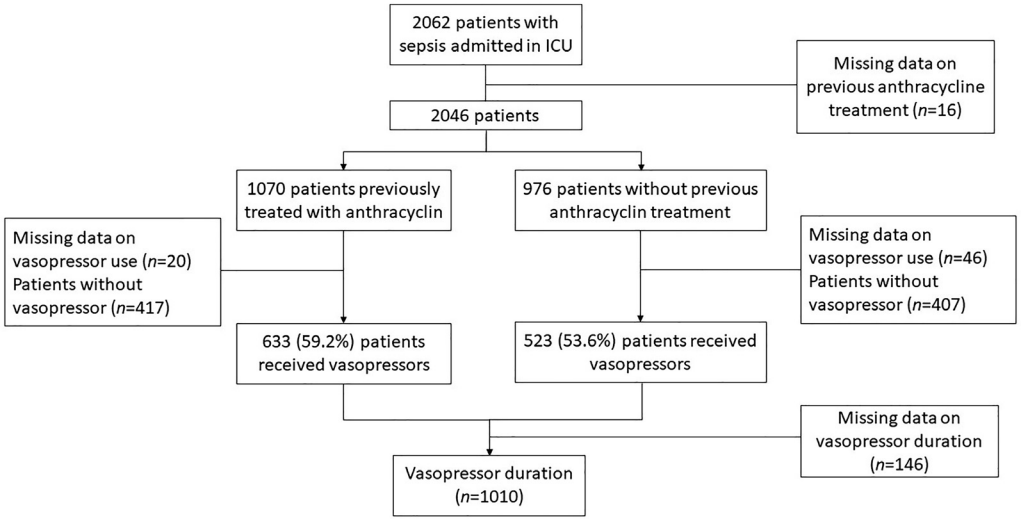

Figure 1. Flowchart of 2046 septic patients admitted in ICU. ICU: Intensive care unit.

49.2%), chronic hematological diseases (*n*=677, 33.1%), and solid tumors (*n*=362; 17.7%). Sepsis was mostly pneumonia (*n*=847/1773, 47.7%), and the median length of symptoms before ICU admission was 2 days (IQR:1–4 days). During ICU stay, 1001 out of 1957 (51.1%) patients received invasive mechanical ventilation, 1156 out of 1980 (58.4%) patients received vasopressors, and 420 out of 1895 (22.1%) patients received RRT. The mean duration of vasopressors was 3 days (IQR: 2–6 days). Notably, 1070 (52.3%) patients received anthracycline for cancer treatment and 976 (47.7%) patients did not. Comparisons between patients who received anthracycline and those who did not are summarized in Table 1.

Table 1
Characteristics of patients with or without previous anthracycline treatment.

Variables	Overall		No anthracycline		Anthracycline		*P*-value
	n	Data	*n*	Data	n	Data	
Age (years)	2046	59 (48–67)	976	62 (52–70)	1070	56 (45–65)	<0.001
Female	2046	794 (38.8)	976	352 (36.1)	1070	442 (41.3)	0.02
Arterial hypertension	1678	431 (25.7)	822	244 (29.7)	856	187 (21.8)	<0.001
At least one comorbidity	1903	1031 (54.2)	923	508 (55.0)	980	523 (53.4)	0.02
Underlying disease							<0.001
Acute malignant hematological disease	2046	1007 (49.2)	976	131 (13.4)	1070	876 (81.9)	
Chronic hematological disease	2046	677 (33.1)	976	530 (54.3)	1070	147 (13.7)	
Solid tumor	2046	362 (17.7)	976	315 (32.3)	1070	47 (4.4)	
Metastatic status for solid tumor*	279	174 (62.4)		NA		NA	
Remission*	907	248 (27.3)		NA		NA	
Allogeneic stem cell transplant	1837	249 (13.6)	869	101 (11.6)	968	148 (15.3)	0.04
Aplasia at ICU admission	1560	637 (38.8)	697	213 (30.6)	863	424 (49.1)	<0.001
Duration of symptoms before ICU	1583	2 (1–4)	750	2 (1–4)	833	2 (1–4)	0.33
Lactate dosage >2 mmol/L*	903	472 (52.3)		NA		NA	
Lactate*	903	2.1 (1.3–4.0)		NA		NA	
SOFA total at ICU admission	2046	7 (4–10)	976	6 (4–9)	1070	7 (4–10)	0.002
Invasive treatment during ICU							
Mechanical ventilation	1957	1001 (51.1)	911	457 (50.2)	1046	544 (52)	<0.001
Mechanical ventilation duration		4 (0–11)		3 (0–8)		6 (1.25–12.00)	<0.001
Vasopressor needs	1980	1156 (58.4)	930	523 (56.2)	1050	633 60.3)	<0.001
Vasopressor duration		3 (2–6)		1 (0–2)		2 (0–4)	0.02
RRT	1895	420 (22.1)	906	178 (19.6)	989	242 (24.5)	0.04
RRT duration		2 (1–6)		2 (1–6)		1 (1–5)	0.47
Sepsis included†							
Pneumonia	1773	847 (47.7)	776	361 (46.5)	997	486 (48.7)	<0.001
Catheter-related infection	809	58 (7.1)		NA		NA	
Other infection	2046	1292 (63.1)	976	678 (69.45)	1070	614 (57.3)	<0.001
Hospital-acquired infection during ICU stay	1485	247 (16.6)	710	121 (16.8)	775	126 (16.2)	0.70
End-of-life decision*	1327	287 (21.6)		NA		NA	
LOS in hospitalization before ICU	1784	2 (1–4)	842	2 (0–11)	942	10 (1–21)	<0.001
Mortality at ICU discharge	1876	642 (34.2)	855	280 (32.7)	1021	362 (35.4)	<0.001
Day 30 mortality	1341	723 (53.9)	651	336 (50.6)	650	387 (59.5)	<0.001

Data are expressed as median (interquartile range) or *n* (%), and the age of the patients was expressed as median (range).
ICU: Intensive care unit; LOS: Length of stay; NA: Not available; RRT: Renal replacement therapy; SOFA: Sequential organ failure assessment.
* No statistics were performed for variables with >30 % missing data. *P*-value included missing data.
† Patients may have more than one source of sepsis. Source of sepsis was not described in all the studies.

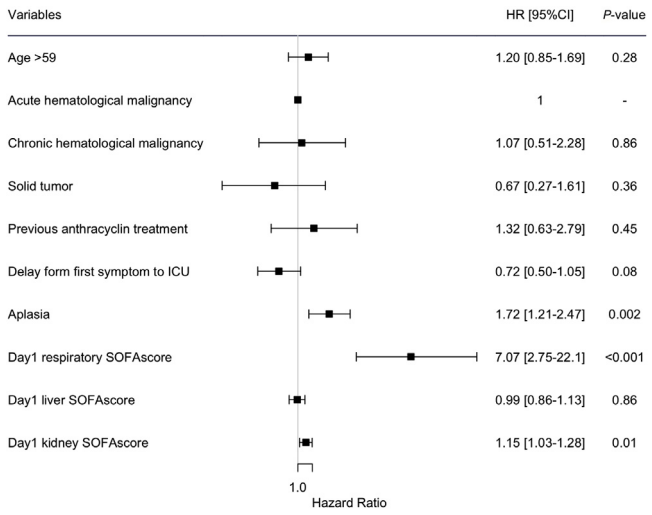

Figure 2. Forest plot of multivariate logistic model for risk factors associated with the risk of vasopressor needs. Day 1 modified SOFA score = Day 1 SOFA score excluding hemodynamic SOFA score.
CI: Confidence interval; HR: Hazard ratio; ICU: Intensive care unit; SOFA: Sequential organ failure assessment.

Comparisons between patients who received vasopressors during ICU stay (regardless of the time after ICU admission) are summarized in Supplementary Table S2.

Multivariate analysis

Multivariate analysis, including all characteristics on the first day of ICU admission, showed no association between previous anthracycline treatment and the need for vasopressors (Figure 2). Similarly, previous anthracycline treatment was not associated with mortality (odds ratio [OR]=0.65, 95% confidence interval [CI]: 0.24 to 1.60, *P*=0.36) (Supplementary Figure S1).

PS

After PS matching, the covariates were well-balanced between the two groups of the PS population (Supplementary Figure S1). In the PS population, multivariate analysis, including confounders associated with sepsis severity (SOFA score without hemodynamic score, at least one comorbidity, aplasia, duration of symptoms before ICU admission), found no association between previous anthracycline treatment and catecholamine requirement (OR=1.38, 95% CI: 0.97 to 1.95, *P*=0.07). In the PS population, previous anthracycline treatment was also not associated with higher ICU mortality (OR=1.13, 95% CI: 0.93 to 1.37, *P*=0.20).

Of the 1156 patients who received vasopressors, 633 (54.0%) had previously received anthracycline. Excluding 146 patients without data on vasopressor duration (Figure 1), the vasopressor duration was not different between the two groups in the PS population using a competing risk analysis for the adjusted SOFA score on day 1 (*P*=0.79) (Figure 3).

Discussion

This study confirmed that previous anthracycline treatment did not affect the course of sepsis in a cohort of cancer patients admitted to the ICU with sepsis.

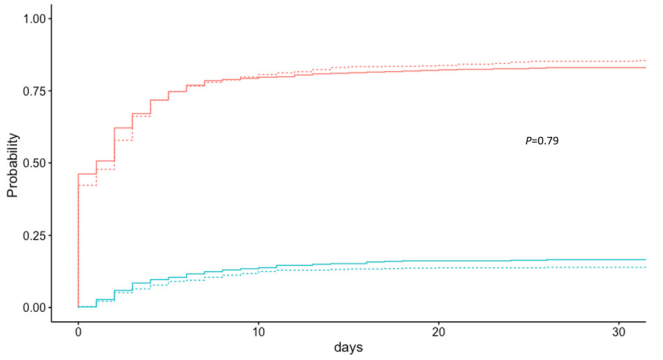

Figure 3. Duration of vasopressor infusion in patients with or without previous treatment with anthracycline. Dashed lines: patients with previous treatment with anthracycline. Plain lines: patients without previous treatment with anthracycline. Blue lines: patients who died while vasopressor infusion. Red lines: patients who were alive at the end of vasopressor infusion.

The risk of sepsis in patients with cancer has been estimated to be 10 times higher than in patients without cancer, with high variability between cancer subtypes.[4] Hematological malignancies, particularly acute leukemia, myeloma, and breast cancer, have the highest risk of sepsis.[35] Among patients admitted to the ICU for sepsis, 15%–20% were patients with malignancy in recent observational cohorts.[20,21,36] In addition to its effects on the immune system, chemotherapy may alter the functions of other organs and tissues, limiting their ability to adapt to aggression. Acute circulatory failure in patients with cancer and sepsis is often associated with anemia and cardiac dysfunction.[7,22] In recent decades, the increasing use of intensive curative regimens and advances in supportive care have improved outcomes and prolonged survival in cancer patients. However, this increase in survival has been achieved at the cost of an increased incidence of infectious and treatment-related complications.[23,24] Sepsis is a life-threatening condition driven by an ongoing infectious process responsible for an uncontrolled systemic inflammatory response, ultimately leading to acute circulatory and multiorgan failure.[25] It is associated with a high mortality rate of approximately 30%–40%.[25,26] In cancer patients, ICU mortality can be as high as 50%.[8,27] However, the respective contribution of the underlying malignancy and the severity of the shock has never been properly assessed. In fact, the disease- and treatment-related immunodeficiencies may explain the increased mortality.[28] In sepsis, the observed hypotension can be related to three different mechanisms: hypovolemia, cardiac dysfunction, and vascular dysfunction.[29,30] Cancer and therapy-related conditions can exacerbate each of these mechanisms in cancer patients: neutropenic enterocolitis itself can induce hypovolemia; chemotherapy can lead to cardiac dysfunction through oxidative stress[37,38]; both chemotherapy and the disease itself can damage endothelial cells and promote vascular dysfunction during sepsis.[39,40] These conditions may contribute to the greater severity of sepsis in cancer patients. Cytostatic endothelial toxicity is thought to be associated with impaired vascular response to vasopressors and microcirculatory changes, although there is no clear clinical evidence.[41] In this setting, anthracycline may be a drug with multiple effects on cardiac, endothelial, and immune dysfunction. Although this study confirmed the higher risk of needing vasopressors in patients who had previously received anthracycline, there was no effect on the outcome during shock. A previous monocentric

study by our group compared 82 patients receiving chemotherapy prior to sepsis with 20 newly diagnosed cancer patients not receiving chemotherapy and 45 control patients without cancer. The maximum dose and mean duration of norepinephrine did not differ between groups.[41] Our multicenter study with >1000 patients confirmed this result. Contrary to the hypothesis, anthracycline did not increase the severity of the hemodynamic response to sepsis. This finding may be important when deciding whether to admit patients to intensive care. Although this result is surprising, several hypotheses can be made. First, all included patients received multiple chemotherapy regimens prior to ICU admission. The design of the database and the study could not distinguish the effect of each chemotherapy regimen. Other chemotherapy drugs received might have an effect on the course of sepsis. Second, the severity of sepsis may be related to several factors, including the source of sepsis, the prompt treatment of sepsis, illustrated in our data by the short delay of antibiotics onset or ICU admission after the first symptoms, and the course of the underlying disease. The strengths of our study were its multicenter nature and the large number of patients included. The main cause of sepsis was pneumonia, which remains one of the most common and severe sepsis in immunocompromised patients.[42] Catheter-related sepsis, which can be rapidly reversible, was present in only 2.9% of patients. In this setting, the population studied reflected the real-world population of cancer patients in the ICU. In addition, the delay from sepsis to ICU admission was quite short and reflected the experience of the ICUs included in the research group. Indeed, prompt admission and treatment of such patients have been associated with lower mortality.[43] In this setting, Vandijck et al.[44] reported no impact on outcomes in patients with sepsis who received chemotherapy, probably because of patient selection and prompt antibiotic treatment. Similarly, pre-admission triage of cancer patients most likely to benefit from ICU management resulted in the admission of a large proportion of young people with no or few comorbidities.[45] In these selected patients, sepsis-associated mortality may be more related to the sepsis itself and its prompt management than to cancer-related characteristics.

Our study has several limitations.[41] First, it was a retrospective study and only patients admitted to the ICU were analyzed. Such patients were selected with the highest benefit of ICU admission. Patients who developed sepsis while receiving anthracycline and were not admitted to the ICU because they were too severe or because they improved on the ward could not be analyzed. Triage may change the outcome of sepsis in patients who received anthracycline. Along the same idea, pre-admission triage of cancer patients, who are most likely to benefit from ICU management, resulted in the admission of a large proportion of young people with no or few comorbidities,[45] which is likely to have influenced our results. However, the design and the large number of patients enrolled seemed to be appropriate for the main objective of the duration of vasopressors in sepsis. Second, although the PS analysis reduced the bias related to anthracycline treatment, some other unknown confounding factors may have influenced the results, such as the anthracycline dose received before ICU admission. Third, we cannot exclude that our study failed to detect a difference in the use of norepinephrine infusion between groups due to missing data and unknown confounders. However, the large number of patients may be informative. Fourth, lactate levels were missing in several studies, and patients with septic shock could not be separated from patients with sepsis-associated hypotension. This limitation may have an impact on the duration of vasopressors. However, the severity of sepsis was assessed using the SOFA score. Finally, our results were obtained in highly experienced, high-volume cancer centers and may not be reproducible in other settings.

Conclusions

In conclusion, this study confirms that anthracyclines have no effect on the course of sepsis in a cohort of cancer patients admitted to the ICU. Further studies, including experimental studies with echographic features, are warranted to confirm this finding.

CRediT Authorship Contribution Statement

Camille Windsor: Writing – review & editing, Writing – original draft, Methodology, Formal analysis, Conceptualization. **Adrien Joseph:** Formal analysis, Conceptualization. **Stephanie Pons:** Conceptualization. **Djamel Mokart:** Supervision, Conceptualization. **Frederic Pène:** Supervision. **Achille Kouatchet:** Supervision. **Alexandre Demoule:** Supervision. **Fabrice Bruneel:** Supervision. **Martine Nyunga:** Supervision. **Edith Borcoman:** Supervision. **Matthieu Legrand:** Supervision. **Michael Darmon:** Supervision, Methodology, Formal analysis. **Lara Zafrani:** Supervision, Conceptualization. **Elie Azoulay:** Supervision, Conceptualization. **Virginie Lemiale:** Validation, Supervision, Methodology, Formal analysis, Data curation, Conceptualization.

Acknowledgments

Groupe De Recherche Respiratoire En Réanimation Onco-Hématologique.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Ethics Statement

All the studies included in the merged database were approved to IRB or local ethic committee according to the French law at the time of the study (Supplementary Table S2).

Conflict of Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data Availability

All data generated or analyzed during this study are included in this published article and its supplementary information files.

Supplementary Materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.jointm.2024.07.005.

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