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Journal of Critical and Intensive Care

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AIMS AND SCOPE

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Journal of Critical and Intensive Care (J Crit Intensive Care) is the scientific and official publication of the Society of Turkish Intensivists (STI) (www.tuyud.org.tr). The Journal is an international open access journal, published 3 times a year (April, August, December). All processing is conducted through the online submission system on the web site: www.jcritintensivecare.org. Manuscripts are accepted for publication through an independent unbiased and double-blinded peer review process. Only manuscripts written in English are accepted and only unpublished manuscripts that are not under review for publication elsewhere can be submitted. Journal of Critical and Intensive Care does not accept multiple submissions even though the previous one was published in a different language.

The 'Journal of Critical and Intensive Care Article Evaluation Flow' is included under **Editorial Policies** tab.
The Journal's aim is to publish qualified research material on the field of intensive/critical care medicine. As well, it aims to facilitate sharing of experience and knowledge through invited reviews and case reports of rare conditions.

Original clinical, basic and translational research articles, case reports and letters to the editor related to intensive/critical care medicine including pediatric intensive care; neurointensive care; intensive care nursing, physiotherapy, respiratory therapy, nutrition and pharmacology in intensive care, as well as acute and emergency medicine are being published. Editorials and review articles are only accepted upon invitation of the editor. The target group of Journal of Critical and Intensive Care is physicians and healthcare staff at clinical and basic science departments who are interested in intensive care.

ABSTRACTING AND INDEXING

Journal of Critical and Intensive Care is indexed in Web of Science Emerging Sources Citation Index (ESCI), TUBITAK ULAKBIM TR Index, EMBASE, Scopus, EMCare, CINAHL, Gale/Cengage Learning, EBSCO, HINARI, OUCI, SCILIT, ProQuest, ASCI and Turkiye Citation Index.

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Journal of Critical and Intensive Care

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After an initial screening by the technical secretary, an editor is assigned for the manuscript. An external and independent editor is invited by the Editor-in-Chief for the evaluation processes of manuscripts submitted by the editorial board members of the journal.

The Editor receives an email inviting him/her to assess the new manuscript. On receiving a manuscript, editors should ascertain if it is potentially suitable for publication. iThenticate Similarity Check report is evaluated. Any manuscript found to be unsuitable may be rejected immediately.

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Manuscripts which are found suitable for double blind peer-review are assigned to at least two independent reviewers who are experts in the field. For this purpose, proposed reviewers by the authors may or may not be assigned. Care is undertaken not to assign undesired reviewers if stated in the cover letter. Upon receipt of all peer review reports a decision is made for the article. The editors take into account both the reviewer reports and their own view of the manuscript.

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A full informed consent must be obtained from the participants of prospectively designed studies and case reports even if the research is non-interventional. In retrospectively designed studies informed consent could be waived but ethical or institutional review board approval is mandatory,

The entire editorial process of article review is carried out using the journal's online article tracking system. "Journal of Critical and Intensive Care Article Evaluation Flow" is as follows.

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Journal of Critical and Intensive Care

INSTRUCTIONS FOR THE AUTHORS

Journal of Critical and Intensive Care (J Crit Intensive Care) is the scientific and official publication of the Society of Turkish Intensivists (www.tuyud.org.tr).

The journal is an open access journal, published 3 times a year and all of its contents are freely available with no cost and there is no fee for submission. It accepts manuscripts written only in English and evaluates submissions through its online submission system on the web site www.jcritintensivecare.org. It publishes original clinical, basic and translational research articles, case reports and letters to the editor related to intensive/critical care medicine and acute medicine. Editorials and review articles are only accepted upon invitation of the editor.

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Journal of Critical and Intensive Care

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Letters submitted within 2 months after the publication of an original article in PDF format on the web page, will be accepted, if deemed appropriate, and will be published soon after or in the subsequent volume of the published original article together with author's response.

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- Name and address for corresponding author (including phone, e-mail address)
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- References (see original research article)
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Type of manuscript	Word limit	Abstract word limit	Reference limit	Table and figure limit
Original Article	4000	250 (Structured)	35	6
Review Article	5000	250	70	6
Case Series and Report	1500	150	15	2
Editorial	500	-	10	
Letter to the Editor	500	No abstract	5	1

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Journal of Critical and Intensive Care

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Journal of Critical and Intensive Care (J Crit Intensive Care) aims to publish qualified research material in the field of intensive/critical care medicine. As well it aims to facilitate sharing of experience and knowledge through invited reviews and case reports of rare conditions. The Journal publishes original clinical, basic and translational research articles, case reports and letters to the editor related to intensive/critical care medicine including pediatric intensive care; neurointensive care; intensive care nursing, physiotherapy, respiratory therapy, nutrition and pharmacology in intensive care, as well as acute and emergency medicine. The target group of Journal of Critical and Intensive Care is physicians and healthcare staff at clinical and basic science departments who are interested in intensive care.

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The 'Journal of Critical and Intensive Care Article Evaluation Flow' is included under publisher policies tab.

The Journal publishes the reviewer list every year in the last issue to express the appreciation for the reviewers.

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Case Report

ORIGINAL INVESTIGATION

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Association Between Meropenem Exposure and Necrotizing Enterocolitis in Infants: A Retrospective Cohort Study

Ana Beatriz Dantas Gomes,[1] Flavia Evelyn Medeiros Fernandes,[2] Fabiana Ariston Filgueira,[2] Daniel Paiva Marques,[2] Iris Ucella de Medeiros,[2] Francisca Sueli Monte Moreira,[2] Rand Randall Martins[1]

Abstract

Aim: This study aimed to identify specific antimicrobial agents associated with the development of necrotizing enterocolitis in critically ill neonates and to characterize independent clinical and demographic factors associated with its occurrence in this vulnerable population.

Study Design: This retrospective cohort study included neonates admitted for more than 24 hours to a Brazilian neonatal intensive care unit between January 2020 and December 2021. Only cases of necrotizing enterocolitis classified as Bell stage IIA or higher were analyzed. Antimicrobial exposure was assessed by days of therapy, considering only agents administered before the diagnosis of necrotizing enterocolitis. Univariate and multivariate logistic regression analyses were performed.

Results: Among 594 neonates included, 15 developed necrotizing enterocolitis (incidence: 1.7%). Meropenem exposure was significantly associated with necrotizing enterocolitis (adjusted odds ratio 3.74; 95% confidence interval: 1.14–12.2; p=0.03). Additional associated factors included lower gestational age, lower birth weight, presence of congenital heart disease, *Methicillin-resistant Staphylococcus aureus* detection in blood culture, and prolonged hospitalization. No evidence of multicollinearity was found among variables.

Conclusions: Meropenem exposure prior to necrotizing enterocolitis onset was associated with a higher likelihood of developing the disease. These findings reinforce the importance of judicious use of broad-spectrum antibiotics and careful monitoring of antimicrobial stewardship in neonatal units.

Keywords: Bacterial resistance; Broad-spectrum antibiotics; Meropenem; Necrotizing enterocolitis; Neonatal intensive care units.

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Introduction

Necrotizing enterocolitis (NEC) remains a predominant cause of gastrointestinal morbidity and mortality in preterm neonates.[1] Globally, its incidence is estimated at approximately 7.0% among very low birth weight infants and between 2% to 13% in preterm populations.[1,2] The condition carries significant

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mortality risk, increasing the likelihood of death 16-fold in neonates requiring intensive care.[3] Multiple factors have been associated with NEC development, including prematurity, low birth weight, sepsis, blood transfusions, respiratory distress syndrome, and pneumonia.[4] Of particular pathophysiological importance is prior antibiotic exposure, which has emerged as a significant modifiable factor.[5,6]

In clinical practice, empirical antimicrobial therapy for suspected early-onset sepsis (EOS) in preterm neonates frequently involves broad-spectrum antibiotics.[7] These agents profoundly impact the developing gut microbiome and have been mechanistically linked to NEC pathogenesis.[5,6] Their effects include suppression of beneficial commensal microorganisms, overgrowth of potential pathogens, and induction of dysbiosis, all established mechanisms in NEC development.[3,8] Nevertheless, the relationship between early antibiotic exposure and NEC demonstrates considerable complexity. Current evidence remains conflicting regarding risk stratification by specific antimicrobial agents,[3,8,9] highlighting persistent gaps in our understanding of this critical neonatal complication.

Given the paucity of robust evidence regarding antimicrobial-specific risks, this study primarily aims to identify specific antimicrobial agents associated with NEC development in critically ill neonates. Secondarily, we seek to characterize independent clinical and demographic variables associated with NEC in this vulnerable population.

Materials and Methods

Study Design and Participants

This is a retrospective cohort study that assessed the relationship between the occurrence of NEC and exposure to specific antimicrobials in neonates receiving intensive therapy. The research was conducted in the Neonatal Intensive Care Unit (NICU) of a Maternity School, a reference facility for high-risk pregnancies in Natal, Brazil. The institution has 20 level II neonatal Intensive Care Unit (ICU) beds, approximately 400 admissions per year, and exclusively serves patients from the Unified Health System (SUS). All neonates admitted to the NICU between January 2020 and December 2021 with a hospitalization period longer than 24 hours were eligible. Inclusion required documented exposure to at least one antimicrobial agent during hospitalization. No restrictions were applied regarding gestational age, birth weight, congenital anomalies, or palliative care status. Neonates were excluded if they received only supportive therapies (such as parenteral nutrition, electrolytes, and/or blood products) without antimicrobial exposure, or if they had a diagnosed immunodeficiency. The study was approved by the Ethics Committee of Onofre Lopes University Hospital of The Federal University of Rio Grande Do Norte (Approval Number: 5.173.658, Date: 17.12.2021), in accordance with the Declaration of Helsinki and Resolution No. 466/12 of the Brazilian National Health Council. In line with national regulations for retrospective studies, attempts were made to obtain informed consent from legal representatives by telephone contact. When formal consent could not be obtained after repeated attempts, data access was permitted by the ethics committee.

Data Collection

The data were collected from electronic medical records and microbiological test results. Information recorded included gestational age, birth weight, gender, occurrence of ruptured membranes, Apgar score (Appearance, Pulse, Grimace, Activity, and Respiration) score, clinical diagnoses (cardiac, neurological, renal conditions, congenital malformations, early and late-onset sepsis), and length of hospital stay.

The prescribed antimicrobials and their duration of use were measured in days of therapy (DOT), defined as the administration of any antimicrobial agent, counted once per agent for each 24-hour period.[10] Days of therapy is a preferred measure of antimicrobial consumption in children, as it accounts for differences in dosage related to age and weight.[11] At the study institution, antimicrobial prescribing in the NICU follows strict internal protocols based on national and international guidelines. These include predefined indications for empirical and targeted antimicrobial therapy, daily clinical reassessment, and regular review by the hospital's antimicrobial stewardship team.

Necrotizing enterocolitis was defined according to the modified Bell's criteria, and only cases classified as stage IIA or higher were included in the analysis. These stages correspond to definite NEC, characterized by the presence of at least one clinical sign (e.g., abdominal distension, gastric residuals, bloody stools) combined with radiographic findings such as pneumatosis intestinalis, portal venous gas, or pneumoperitoneum. Cases classified as stage I ("possible NEC"), which involve only non-

specific systemic or gastrointestinal signs without radiographic confirmation, were excluded from this study.[12] For all cases, only antimicrobials administered before the clinical and radiographic diagnosis of NEC were considered as exposure variables in the analysis.

The blood, cerebrospinal fluid, and urine samples used for microbiological characterization were obtained from hospitalized patients at the institution and analyzed in the institution's Microbiology Laboratory. For isolation and characterization, the samples were incubated using an automated system (Phoenix, BD) designed for the rapid detection of bacteria and fungi through a phenotypic method. Resistance markers for extended-spectrum β-lactamases (ESBL) and methicillin-resistant *Staphylococcus aureus* (MRSA) were identified using the same automated methodology. For the phenotypic identification of carbapenemase-producing *Enterobacteriaceae* (KPC), a confirmatory method using the modified Hodge test was employed, although it is no longer recommended due to its low specificity and, in some cases, less than ideal sensitivity.[13] Lastly, the vancomycin resistance marker for *Enterococcus faecium* or *Enterococcus faecalis* (VRE) was identified via strip sensitivity testing using vancomycin.

Statistical Analysis

With a presumed prevalence of 7% for NEC,[2] the sample size was defined as 626 individuals, ensuring a maximum error of ±2 percentage points with 95% confidence. Data analysis was conducted using Stata version 15 (Stata Corporation, College Station, TX, USA). The data were presented as median and interquartile range, absolute and relative frequencies, and mean and standard deviation, depending on the type of variable analyzed. The incidence of NEC was expressed as an incidence rate (number per 1,000 patient-days) with a 95% confidence interval (CI). To compare population characteristics between neonates with and without NEC, normality of continuous variables was first assessed using the Shapiro–Wilk test. Depending on the distribution, either Student's t-test or the Mann–Whitney U test was applied. For categorical variables, Pearson's chi-square test or Fisher's exact test was used. A p-value <0.05 was considered statistically significant.

Univariate logistic regression was used to determine factors associated with the occurrence of NEC, estimating respective odds ratios (OR) and 95% confidence intervals. All variables with an association test showing a p-value <0.10 were included in a multivariate logistic regression model, and a significance level of $p<0.05$ was adopted. The factors identified in the previous stage were used as adjustment variables in investigating the relationship between the DOT of the most prescribed antimicrobials and the occurrence of NEC via a multivariate logistic regression model ($p<0.05$). Collinearity between variables included in the multivariable logistic regression model was assessed using the variance inflation factor (VIF). VIF values remained below the conventional threshold of 5, indicating no relevant multicollinearity among the variables analyzed. Late-onset sepsis cases included in the analysis all occurred prior to the diagnosis of NEC. Cases of sepsis diagnosed concurrently with or after NEC onset were not included as potential risk factors. To assess causality between the initiation of antimicrobial use and the period of NEC diagnosis, Student's t-test was used for mean comparison ($p<0.05$).

AI Use Statement

No generative artificial intelligence (AI) tools were used in the conception, design, data analysis, or writing of this manuscript. All content was produced exclusively by the authors.

Results

During the study period, 594 neonates were included, with a mean gestational age of 33.2±4.4 weeks and a birth weight of 1978.3±1010.2 g (Table 1). Regarding the diagnosis of sepsis, 173 neonates were identified with early-onset sepsis (29.1%), and 206 had late-onset sepsis (34.7%). The length of hospital stay was 24.5±32.3 days, and 15 neonates presented with NEC, corresponding to a cumulative incidence of 1.7%. The incidence rate was 40.85 cases per 1,000 patient-days (95% CI: 22.89–68.47).

In Table 2, the prescription profile of antimicrobials and DOT are described. The combination of ampicillin and gentamicin was the most common prescription (359 neonates, 55.4%), followed by the regimen of oxacillin and ampicillin (200, 33.7%), meropenem (150, 25.3%), and vancomycin (148, 24.9%). Among the most frequently used antimicrobials, meropenem and vancomycin showed the longest durations of use prior to NEC diagnosis, with median durations of 15 and 13 days, respectively. These two agents also stood out for their prevalence among neonates who developed NEC: 13 of the 15 affected neonates had received meropenem, and 14 had received vancomycin prior to NEC onset.

Table 1. Population characteristics (n=594)

Characteristics	Total Feature	Without NEC (n=579)	With NEC (n=15)	p
Gestational age in weeks (Mean±SD)	33.2±4.4	33.3±4.4	30.7±3.7	0.03
Gestational age in weeks (n, %)				
≤28 weeks	108 (18.1%)	103 (17.8%)	5 (33.3%)	0.12
29–35 weeks	290 (48.5%)	282 (48.7%)	8 (53.3%)	0.72
≥36 weeks	196 (33.0%)	194 (33.5%)	2 (13.3%)	0.10
Birth weight in grams (Mean±SD)	1978.3±1010.2	1998.7±1009.4	1191.0±688.9	<0.01
Birth weight in grams (n, %)				
≤1000 grams	118 (19.9%)	111 (19.2%)	7 (46.7%)	<0.01
1001–2500 grams	304 (51.2%)	297 (51.3%)	7 (46.7%)	0.72
≥2501 grams	172 (30.0%)	171 (29.5%)	1 (6.7%)	0.06
Female gender (n, %)	277 (46.9%)	270 (46.9%)	7 (46.7%)	0.98
Ruptured membranes (n, %)	85 (15.7%)	82 (15.5%)	3 (21.4%)	0.55
Apgar score at 1 minute (Mean±SD)	6.4±2.3	6.4±2.3	5.7±2.3	0.51
Apgar score at 5 minutes (Mean±SD)	7.9±1.5	7.9±1.5	7.7±1.6	0.50
Clinical diagnosis (n, %)				
Cardiac diseases	74 (12.5%)	71 (12.6%)	3 (20.0%)	0.37
Malformations	76 (12.8%)	73 (12.1%)	3 (20.0%)	0.40
Neurological diseases	30 (5.1%)	30 (5.1%)	0 (0.0%)	0.37
Renal diseases	46 (7.7%)	43 (7.4%)	3 (20.0%)	0.11
Early-onset sepsis (n, %)				
Clinical diagnosis	163 (27.4%)	159 (27.5%)	4 (26.7%)	0.83
Laboratory diagnosis	10 (1.7%)	10 (1.7%)	0 (0.0%)	0.77
Late-onset sepsis (n, %)				
Clinical diagnosis	101 (17.0%)	99 (17.1%)	2 (13.3%)	0.77
Laboratory diagnosis	105 (17.7%)	95 (16.4%)	10 (66.7%)	<0.01
Bacterial resistance marker (n, %)				
ESBL*	80 (13.5%)	72 (12.4%)	8 (53.3%)	<0.01
MRSA#	44 (7.4%)	39 (6.7%)	5 (33.3%)	<0.01
KPC=	17 (2.9%)	14 (2.4%)	3 (20.0%)	<0.01
Length of hospitalization in days (Mean±SD)	24.5±32.3	24.4±33.5	63.7±35.5	<0.01
Necrotizing enterocolitis (n, IR per 1,000 patient-days, 95% CI)	15; 40.85 (22.89–68.47)	-	-	-
Death (n, %)	83 (14.0%)	76 (13.1%)	7 (46.7%)	<0.01

*ESBL: Extended-Spectrum Beta-Lactamases; #MRSA: Methicillin-resistant *Staphylococcus aureus*; =KPC: Carbapenemase-producing *Enterobacteriaceae*; IR: Incidence Rate. Missing data: sex (n=3), ruptured membranes (n=51), Apgar score at 1 min (n=2), Apgar score at 5 min (n=2), and length of hospitalization (n=8).

Regarding factors associated with the occurrence of NEC (Table 3), univariate analysis identified lower gestational age (OR: 0.956, 95% CI: 0.914-0.999), birth weight (OR: 0.999, 95% CI: 0.998-0.999), congenital heart disease (OR: 1.811, 95% CI: 1.043-3.145), congenital malformations (OR: 1.923, 95% CI: 1.160-3.218), and late-onset sepsis (OR: 3.367, 95% CI: 1.917-5.913). Additionally, the presence of ESBL (OR: 3.586, 95% CI: 2.339-5.496), KPC (OR: 3.357, 95% CI: 1.903-5.923), MRSA (OR: 3.464, 95% CI: 2.197-5.460), and longer hospitalization (OR: 1.007, 95% CI: 1.004-1.010) were associated with NEC. However, the multivariate model confirmed only gestational age (OR: 1.250, 95% CI: 1.134-1.377), birth weight (OR: 0.998, 95% CI: 0.997-0.999), congenital heart disease (OR: 4.777, 95% CI: 2.217-10.293), MRSA (OR: 2.748, 95% CI: 2.067-7.705), and longer hospitalization (OR: 1.004, 95% CI: 1.000-1.008) as related to the occurrence of NEC. The collinearity analysis revealed no evidence of multicollinearity among the variables included in the multivariable model. All VIF values were below 2, supporting the independence of the effects observed (Table 1).

Table 2. Prevalence of antimicrobials, their respective prescription days, and occurrence of necrotizing enterocolitis

Antimicrobial	Neonates		Therapy Days			NEC Occurrence	
	n	%	Median	p25	p75	n	%
Ampicillin + Gentamicin	329	55.4	6	4	8	8	1.3
Oxacillin + Amikacin	200	33.7	7	4	9.5	10	1.7
Meropenem	150	25.3	15	8	25	13	2.2
Vancomycin	148	24.9	13	8.5	19.5	14	2.4
Fluconazole	110	18.5	22	10	33	7	1.2
Penicillin	106	17.8	7	4	9	0	0.0
Cefepime	82	13.8	8	4	12	9	1.5
Amphotericin B	62	10.4	19.5	12	30	6	1.0
Polymyxin	25	4.2	14	4	18	2	0.3
Ciprofloxacin	22	3.7	9	5	15	2	0.3
Piperacillin-Tazobactam	21	3.5	6	3	8	3	0.5
Liposomal Amphotericin B	20	3.4	17	11	22	5	0.8
Others	21	3.5	6	4	11	0	0.0

Table 3. Multivariate logistic regression model to investigate factors associated with the occurrence of necrotizing enterocolitis

Characteristics	Univariate				Multivariate			
	OR	95% CI		p	OR	95% CI		p
Gestational age in weeks	0.956	0.914	0.999	0.049	1.250	1.134	1.377	<0.001
Birth weight in grams	0.999	0.998	0.999	<0.001	0.998	0.997	0.999	<0.001
Female gender	0.885	0.579	1.350	0.570	-	-	-	-
Ruptured membranes	1.161	0.686	1.967	0.576	-	-	-	-
Apgar score at 1 minute	0.964	0.884	1.051	0.413	-	-	-	-
Apgar score at 5 minutes	0.979	0.866	1.107	0.740	-	-	-	-
Patent ductus arteriosus (PDA)	1.733	0.478	6.287	0.403	-	-	-	-
Mechanical ventilation	1.428	0.400	5.097	0.549	-	-	-	-
Clinical diagnosis					-	-	-	-
Cardiac diseases	1.811	1.043	3.145	0.035	4.777	2.217	10.293	<0.001
Malformations	1.923	1.160	3.218	0.011	-	-	-	-
Neurological diseases	1.000	-	-	-	-	-	-	-
Renal diseases	1.525	0.892	2.607	0.123	-	-	-	-
Early-onset sepsis	0.925	0.588	1.456	0.738	-	-	-	-
Late-onset sepsis	3.367	1.917	5.913	<0.001	-	-	-	-
Bacterial resistance marker					-	-	-	-
ESBL*	3.586	2.339	5.496	<0.001	-	-	-	-
KPC=	3.357	1.903	5.923	<0.001	-	-	-	-
MRSA#	3.464	2.197	5.460	<0.001	2.748	2.067	7.705	<0.001
Length of hospitalization in days	1.007	1.004	1.010	<0.001	1.004	1.000	1.008	0.050

*ESBL: Extended-Spectrum Beta-Lactamases; #MRSA Methicillin-Resistant Staphylococcus aureus; =KPC: Carbapenemase-Producing Enterobacteriaceae.

The characteristics identified in the previous model were used as adjustment variables to identify antimicrobials associated with the occurrence of NEC (Fig. 1). Only meropenem (OR: 1.075, 95% CI: 1.006-1.148) and vancomycin (OR: 1.067, 95% CI: 1.003-1.136) were found to be related to NEC. In Figure 2, it is observed that meropenem is commonly prescribed around the 17th day of hospitalization, preceding the diagnosis period of

NEC around the 34th day (17.5, 95% CI: 10.6-24.4 vs. 34.5, 95% CI: 20.3-42.7 days; p=0.03). Despite vancomycin showing a relationship with NEC, the analysis in Figure 2 demonstrates that only meropenem was statistically significant.

Discussion

In this retrospective cohort of 594 neonates, we identified that prior exposure to meropenem was associated with the development of NEC. In addition to previous meropenem use, other independent variables associated with NEC were identified: lower gestational age, very low birth weight, presence of congenital heart disease, MRSA positivity in blood culture, and longer hospital stay. Our findings reinforce this knowledge by further highlighting the potential role of a broad-spectrum antibiotic in this association.

The necrotizing enterocolitis incidence observed in our study (2%) was slightly lower than that reported in previous studies, which range between 2% and 13% in preterm populations. For instance, Alsaied et al.[2] in 2020 estimated a pooled global prevalence of 7% among very low birth weight infants, while Zozaya et al.[1] in 2020 reported an incidence of 8.8%, with 5.5% requiring surgical treatment.We emphasize the use of strict diagnostic criteria for NEC, including only cases classified as Bell stage IIA or higher (modified Bell criteria), with clinical and radiological confirmation.[3,12] By applying this definition, we ensured comparability with most published studies and avoided the inclusion of mild or equivocal cases that could artificially increase incidence estimates. We also documented a high rate of early-onset neonatal sepsis (29.1%) in our cohort—higher than rates typically reported in Brazilian neonatal units.[14] This discrepancy may reflect the use of broader clinical criteria for early-onset sepsis diagnosis and the higher severity profile of

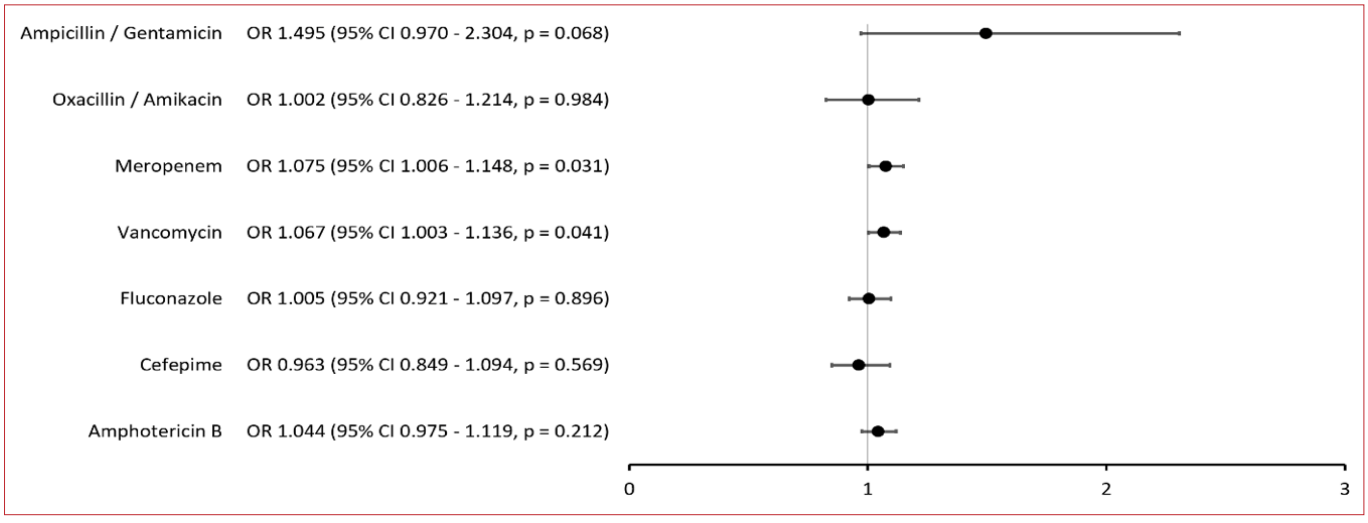

Figure 1. Multivariate logistic regression model investigating antimicrobials associated with the occurrence of necrotizing enterocolitis, adjusted for gestational age, birth weight, diagnosis of congenital heart disease, infection related to the presence of methicillin-resistant Staphylococcus aureus, and treatment days.

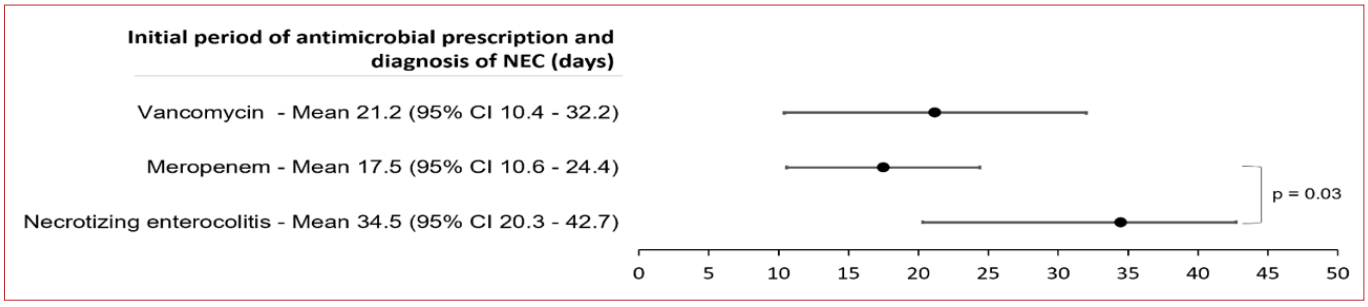

Figure 2. Comparison between the means for the start of antimicrobial administration (meropenem and vancomycin) and the diagnosis period of necrotizing enterocolitis (Student's t-test; p<0.05)*.
***No adjusted analyses were performed; results reflect univariate comparisons.**

patients treated at our referral center. The elevated sepsis rate indicates that a large proportion of patients received empirical antibiotic therapy in the first days of life, a crucial context for interpreting the impact of antimicrobials on subsequent NEC development.

Extensive antibiotic exposure has been consistently associated with NEC, likely due to its disruption of the neonatal gut microbiota. Broad-spectrum antimicrobials may suppress beneficial commensal bacteria and promote dysbiosis, favoring colonization by pathogenic microorganisms.[5,15] In preterm infants, this dysbiosis can trigger mucosal injury and intestinal inflammatory responses, contributing to NEC pathophysiology.[16] Among extremely low birth weight infants, prolonged antibiotic use (≥5 days) for suspected early-onset sepsis is associated with increased NEC incidence.[6,9,17] Our findings expand this evidence by identifying a specific antibiotic—meropenem—as independently associated with NEC. In our cohort, meropenem was initiated, on average, around the 17th day of life, while NEC diagnosis occurred at a median of 34 days. This temporal sequence strengthens the plausibility of a causal association, though it does not confirm it.

Although antibiotic use in general has been previously associated with NEC, few studies have evaluated the association with specific agents. To our knowledge, this is one of the first studies to identify meropenem as independently associated with NEC using a multivariate model. Previously, Raba et al.[9] in 2019 reported a similar association in a case-control study. Our results corroborate these findings in a larger cohort with a study design that better establishes the temporal relationship between antimicrobial exposure and disease development.

It is important to note that meropenem is typically reserved for patients with severe or refractory infections due to its broad-spectrum activity.[18] Thus, its association with NEC may partially reflect the underlying severity of patients who receive it. However, by adjusting for variables such as gestational age, birth weight, and comorbidities, we sought to control for these potential confounders. The persistence of the association even after adjustment suggests that meropenem (or the clinical circumstances warranting its use) may directly contribute to NEC development. Given its broad spectrum of activity against gram-negative, gram-positive, and anaerobic bacteria,[20] its impact on the neonatal intestinal ecosystem is likely substantial.

Our study also identified other factors associated with NEC. Prematurity and low birth weight showed strong associations with the disease, consistent with extensive literature.[1-6,8,9] These factors are linked to immaturity of the intestinal barrier, mesenteric perfusion, and immune system.[5,16] Moreover, extremely preterm infants often require invasive interventions and early antibiotic use, which may compound the risk of gut dysbiosis and NEC.[6,20,21] In this context, MRSA colonization may reflect a history of prolonged broad-spectrum antimicrobial use, commonly associated with resistant organism colonization in NICUs.[22,23] Such colonization indicates an imbalanced microbiota, a central feature in NEC pathophysiology.[5,15] Thus, MRSA likely acts not as a direct causative agent but rather as an indirect marker of intense antimicrobial pressure and gut dysbiosis. Congenital heart disease emerged as another associated factor, supporting previous studies reporting higher NEC incidence even among term infants with cardiac conditions.[24] Finally, prolonged hospitalization was associated with NEC, as expected, since extended hospital stays reflect greater clinical severity, increased exposure to nosocomial infections, and repeated cycles of antibiotic therapy.

The results underscore the importance of vigilant use of broad-spectrum antibiotics in NEC prevention. In clinical practice, this requires careful evaluation of meropenem initiation criteria in neonates and prompt discontinuation when feasible. Identifying empirical regimens with lower impact on the gut microbiota and their association with NEC, as suggested by other authors,[8,20] would be ideal. Concurrently, protective strategies like exclusive breastfeeding, a key factor for intestinal health promotion and consistently associated with lower NEC incidence,[25] should be encouraged.

Several limitations should be considered when interpreting our findings. First, this was a single-center retrospective study, which may restrict generalizability beyond our institutional context. Additionally, the final sample size did not reach the originally planned number of neonates, mainly due to logistical barriers in data collection, and this shortfall may have reduced statistical power and the precision of estimates. Although strict diagnostic criteria were applied, NEC diagnosis relied on a single neonatologist without independent review, and the possibility of misclassification with spontaneous intestinal perforation cannot be completely excluded. The inclusion of neonates with congenital anomalies and those receiving palliative

care may also have influenced clinical management and outcomes. Moreover, important clinical variables such as feeding type, blood product transfusions, and validated severity-of-illness scores were not available for analysis, which limited adjustment for established NEC risk factors. Another limitation is the absence of stratified analyses by gestational age or birth weight, and survivor bias may explain the unexpectedly higher NEC incidence at greater gestational ages, as extremely preterm neonates often died before the typical onset window. Regarding antimicrobial exposure, cumulative or combined use of broad-spectrum agents was not formally analyzed, and confounding by indication remains a concern, since meropenem was frequently prescribed to more severely ill neonates. Finally, local antimicrobial stewardship policies may have influenced antibiotic prescribing patterns, thereby limiting the external validity of our results. Despite these limitations, our study contributes valuable preliminary evidence by evaluating recent data from a tertiary NICU with standardized antimicrobial protocols and advanced neonatal care, which enhance the internal validity of the findings.

Conclusion

In summary, this study identified prior meropenem exposure as an independent associated factor for NEC, alongside established factors including lower gestational age, very low birth weight, congenital heart disease, MRSA infection, and prolonged hospitalization. These findings support the hypothesis that broad-spectrum antibiotics—particularly meropenem—may promote gut dysbiosis and NEC pathogenesis, underscoring the need for judicious use of these agents in neonates. Future research should investigate the underlying pathophysiological mechanisms and validate these associations across diverse populations.

Ethics Committee Approval: Ethics committee approval was obtained from Ethics Committee of Onofre Lopes University Hospital of The Federal University of Rio Grande Do Norte (Approval Number: 5.173.658, Date: 17.12.2021).

Informed Consent: Informed consent from legal representatives by telephone contact.

Conflict of Interest: The authors have no conflicts of interest to declare.

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ORIGINAL INVESTIGATION

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Association Between STAT Mortality Score and Noninvasive Ventilation Failure After Congenital Heart Disease Surgery in Children

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Abstract

Aim: The aim of this study is to determine whether there is an association between STAT (Society of Thoracic Surgeons–European Association for Cardio-Thoracic Surgery) metrics and noninvasive ventilation (NIV) failure, and to describe the factors influencing this outcome in pediatric patients undergoing congenital heart disease (CHD) surgery at a federal referral hospital.

Study Design: This analytical cross-sectional study included patients under 18 years of age with CHD who underwent corrective or palliative surgery and required postoperative NIV support between January 2020 and December 2022. The type of ventilation (prophylactic or therapeutic NIV) was determined by the multidisciplinary clinical team based on surgical complexity, hemodynamic stability, and the patient's respiratory status. Continuous quantitative and dichotomous qualitative variables were analyzed using descriptive and inferential statistics (multivariate logistic regression). The R statistical package, version 4.4.1, was used with a 95% confidence level.

Results: A total of 110 patients (mean age: 18 months; mean weight: 8 kg) met the inclusion criteria. NIV failure occurred in 21% of cases, predominantly due to respiratory causes. STAT Categories 2, 3, 4, and 5 showed no statistically significant association with NIV failure ($p>0.05$). Clinical relevance was noted for NIV duration (odds ratio [OR]=1.06), mechanical ventilation duration (OR=1.01), and intensive care unit (ICU) length of stay (OR=1.01).

Conclusions: No significant association was found between the STAT Mortality Score and Categories and NIV failure. Although mechanical ventilation duration, NIV duration, and ICU length of stay showed a weak positive association (OR=1.01–1.06), these values indicate minimal clinical impact. These findings suggest that while STAT metrics may assist in patient risk stratification, other postoperative factors play a greater role in predicting NIV failure.

Keywords: Congenital; Health care; Heart defects; Noninvasive ventilation; Postoperative period; Quality indicators.

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Introduction

Congenital heart diseases (CHD) encompass a wide range of structural cardiac abnormalities.[1] Approximately 80% of patients with CHD require surgical intervention during their lifetime, and about half of these procedures occur within the first year of life, either for corrective or palliative purposes.[2]

In the early 2000s, researchers developed several tools to assess outcomes following CHD surgery.[3-4] Among them, the Risk Adjustment for Congenital Heart Surgery (RACHS-1) categories and the Aristotle Basic Complexity (ABC) levels became widely used.[1] However, because these classifications were primarily based on expert opinion, they presented limitations in objectively reflecting clinical outcomes.[1] To address this gap, an empirically derived model—the Society of Thoracic Surgeons–European Association for Cardio-Thoracic Surgery (STAT) Mortality Score and Categories—was introduced, providing more accurate and data-driven outcome predictions.[5] This model was later refined to reflect contemporary results.[1]

Based on estimated mortality rates, each surgical procedure receives a numerical score ranging from 0.1 to 5.0, subsequently grouped into five risk categories[5] (Table 1). Category 1 represents the lowest mortality risk (0.2%–1.3%), while Category 5 indicates the highest (13.5%–38.7%).[1-5] The STAT metrics have since been widely adopted in clinical research and quality improvement initiatives.[6-8]

Surgical outcomes in CHD patients depend not only on the anatomical complexity of the defect but also on preexisting conditions and postoperative clinical progression.[9] Mechanical ventilation plays a crucial role in maintaining hemodynamic stability; however, prolonged ventilation may negatively impact recovery.[10] Numerous studies emphasize the benefits of early extubation in reducing complications and shortening intensive care unit (ICU) stays.[11] Nonetheless, patients remain at risk for post-extubation respiratory failure,[12] and noninvasive ventilation (NIV) serves as an important supportive therapy in this context.

NIV helps preserve the cardiopulmonary advantages of positive pressure ventilation while reducing respiratory failure and reintubation rates.[13] However, when NIV fails, escalation to invasive mechanical ventilation becomes necessary, leading to longer ICU stays and increased mortality.[14-15]

Given this clinical relevance, this study aimed to assess whether there is an association between the STAT Mortality Score and Categories and NIV failure in pediatric patients undergoing surgery for congenital heart disease at a federal referral hospital. Additionally, it sought to identify the clinical factors influencing this outcome.

Materials and Methods

This analytical cross-sectional study evaluated both the exposure factor (STAT Mortality Score and Categories) and the outcome (noninvasive ventilation failure) simultaneously. The study was conducted at a specialized referral center for congenital heart diseases, covering the period from January 1, 2020, to December 31, 2022. The outcome, NIV failure, was defined as the need for orotracheal intubation during prophylactic or therapeutic noninvasive support, regardless of the duration of NIV use.

The study was approved by the from Ethics Committee of National Institute of Cardiology (Approval Number: 68156623.5.0000.5272, Date: 31.03.2023), and all procedures complied with the principles of the Declaration of Helsinki. Due to the study's retrospective nature, informed consent was not applicable or required by the ethics committee. We did not use artificial intelligence in the production of this research.

Table 1. Examples of procedures included in the STAT Mortality Score and Categories

STAT Category	Representative Procedures	STAT Score Range	Estimated Mortality Risk (% range)
1	ASD repair, VSD repair, Coarctation repair	0.1–0.3	0.2–1.3
2	Bidirectional Glenn, Fontan procedure, Rastelli	0.3–0.5	1.4–2.6
3	Arterial switch operation, Tetralogy of Fallot with conduit	0.6–0.9	2.7–5.0
4	AVSD complete repair, Norwood stage I	1.0–1.4	6.0–12.0
5	Complex single-ventricle palliation, Cardiac transplant	2.1–5.0	13.5–38.7

ASD: Atrial Septal Defect; AVSD: Atrioventricular Septal Defect; VSD: Ventricular Septal Defect.

Study Population

Patients under 18 years of age with congenital heart disease who underwent corrective or palliative cardiac surgery and required postoperative NIV support were eligible for inclusion.

Exclusion criteria included patients transferred to another hospital while still on NIV and those who remained on noninvasive support after the study period.

Ventilation Type Selection Criteria

The decision regarding the type of noninvasive ventilation—prophylactic (initiated immediately after extubation to prevent respiratory failure) or therapeutic (initiated in response to clinical signs of respiratory distress)—was made by the multidisciplinary intensive care team. This decision was based on factors such as:

- the complexity of the surgical procedure,
- the patient's hemodynamic stability, and
- their pre- and postoperative respiratory condition.

This individualized approach ensured that ventilatory management reflected real clinical practice, allowing evaluation of the STAT score as a complementary predictor of NIV outcomes.

Sample Size

Sample size was calculated using WinPepi version 3.18, a public-domain statistical package for epidemiological analysis. Based on a previously reported NIV requirement prevalence of 21.4%,[13] a 5% margin of error, and a 95% confidence level, the minimum estimated sample size was 33 participants.

Data Collection

Patient data were obtained from a prospectively maintained institutional database containing clinical information collected throughout hospitalization. The database, securely stored in the cloud, is accessible to the multidisciplinary team upon request.

Variables were classified as either continuous quantitative or categorical qualitative:

- Continuous variables: age, weight, duration of mechanical ventilation, duration of NIV, and ICU length of stay.
- Categorical variables: sex, STAT category and score, type of surgery (corrective or palliative), presence of diaphragmatic paralysis, ventilatory status before and immediately after surgery, open chest status, use of extracorporeal membrane oxygenation (ECMO) in the immediate postoperative period, post-extubation ventilatory status (room air, oxygen therapy, or NIV), type of NIV (continuous positive airway pressure [CPAP] or bilevel), causes of NIV failure (respiratory, hemodynamic, infectious, or neurological), and final hospital outcome (ICU, discharge to ward, transfer, or death).

Statistical Analysis

Descriptive and exploratory analyses were performed using absolute (n) and relative (%) frequencies, measures of central tendency (mean and median), and measures of dispersion (standard deviation). The chi-square test, t-test, and Mann–Whitney U test were used as appropriate. Statistical significance was set at $p \leq 0.05$, with a 95% confidence interval.

For inferential analysis, a multivariate logistic regression model was applied to evaluate factors associated with NIV failure, adjusting for potential confounders. The effects of the association between STAT metrics and NIV failure, for variables with significance below 5% in the statistical tests, were included in the multivariate logistic regression model. We conducted the statistical analyses using the R statistical package, version 4.4.1.

Results

Of the 640 patients initially screened, 77% underwent corrective or palliative cardiac surgery. Among these, 111 met the inclusion criteria. One patient was excluded due to transfer to another hospital unit while still receiving NIV support, resulting in a final sample of 110 patients (Fig. 1).

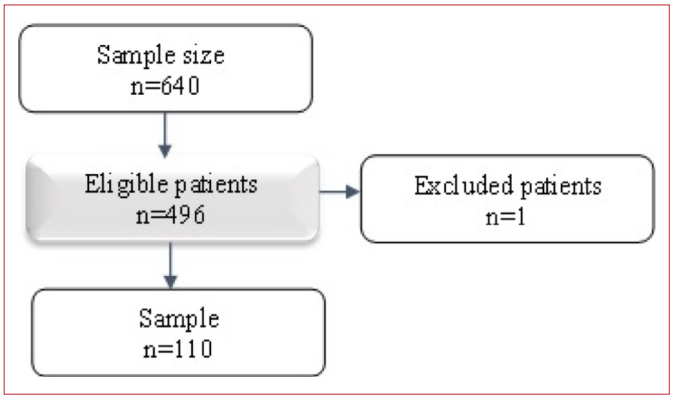

Figure 1. Patient recruitment process flowchart.

Study Patients' Characteristics

As shown in Table 2, most patients were male, with a mean age of 18 months and a mean weight of 8 kg. No single STAT category predominated; patients were distributed across all five risk categories, ranging from 4.54% to 37.27%.

- In Category 1, the most frequent score was 0.1.
- In Category 2, the predominant score was 0.3.
- In Category 3, it was 0.9,
- In Category 4, 1.2.
- In Category 5, 3.0.

Corrective surgeries were more frequent than palliative ones. Most patients required mechanical ventilation preoperatively and immediately postoperatively, with a mean duration of less than 12 days. Following extubation, NIV was the most commonly used ventilatory modality, predominantly in the bilevel mode. Nearly 90% of patients were successfully discharged to the ward, with one recorded death.

NIV failure occurred in 21% of patients. Compared to those with successful NIV, the failure group was characterized by younger age, lower weight, and longer durations of mechanical ventilation, NIV use, and ICU stay. Approximately 40% of the patients who experienced NIV failure belonged to STAT Category 2, most commonly with a score of 0.3. Corrective cardiac surgery, pre-surgical intubation, and discharge to the ward as the final hospital outcome were predominant characteristics in this group.

The main causes of NIV failure were:

- Respiratory factors (60.87%),
- Hemodynamic factors (21.74%),
- Infectious causes (8.69%),
- Neurological causes (4.35%), and
- A combination of respiratory and hemodynamic factors (4.35%).

Logistic Regression Analysis

A multivariate logistic regression model was applied to estimate the likelihood of NIV failure according to clinical characteristics (Table 3). None of the variables reached statistical significance ($p<0.05$). However, clinical relevance was observed for the duration of mechanical ventilation, NIV duration, and ICU length of stay. Specifically, each additional day of NIV use increased the likelihood of failure by 6% (odds ratio [OR]=1.06).

Discussion

This analytical cross-sectional study examined the prevalence of noninvasive ventilation failure and the clinical factors associated with it in pediatric patients undergoing congenital heart disease surgery. Additionally, it investigated whether the STAT Mortality Score and Categories were associated with NIV failure.

The observed NIV failure rate (21%) was comparable to findings in previous studies. Ódena et al.,[16] Yañez et al.,[17] Lum et al.,[18] Pancera et al.,[19] and Gupta et al.[20] reported failure rates around 30%, while Fernández Lafever et al.[13]—whose study design and patient population closely resemble ours—reported a 15% failure rate in pediatric cardiac surgery patients.

The incidence of NIV failure in postoperative pediatric cardiac populations tends to be higher than in other pediatric groups.[21-26] Several factors contribute to this, including younger age, hemodynamic instability, increased extubation failure rates, and the presence of genetic syndromes.[27]

Positive pressure ventilation has well-known cardiovascular effects. Increased intrathoracic pressure can raise ventricular afterload, pulmonary vascular resistance, and myocardial oxygen demand.[13,28] These changes may compromise hemodynamics in children recovering from cardiac surgery, leading to NIV failure in vulnerable patients.

Early extubation in pediatric cardiac surgery has been widely studied and is associated with improved outcomes.[29] However, orotracheal intubation in the immediate postoperative period remains common due to surgical complexity, young age, low weight, preoperative critical illness, respiratory failure, or infections.[29,30] In this study, patients in the NIV failure group were generally younger and lighter, and most had required mechanical ventilation immediately postoperatively. These factors likely contributed to prolonged ventilation, longer ICU stays, and an increased risk of NIV failure—relationships that demonstrated clinical relevance in our analysis, despite lacking statistical significance.

Table 2. Study patients' characteristics

Variable	Total (n=110)	NIV Failure (n=23)	No NIV Failure (n=87)
Male gender, n (%)	61 (55.45)	9 (39.13)	52 (59.77)
Age (months), Mean±SD (median)	18.62±40.16 (3)	10.64±31.86 (3)	20.76±42.01 (2.5)
Weight (kg), Mean±SD (median)	8.16±10.84 (4.1)	5.51±6.75 (3.8)	8.85±11.61 (4.2)
STAT Categories, n (%)			
Category 1	25 (22.73)	5 (21.74)	20 (22.99)
Category 2	41 (37.27)	9 (39.13)	32 (36.78)
Category 3	14 (12.73)	2 (8.7)	12 (13.79)
Category 4	25 (22.73)	6 (26.09)	19 (21.84)
Category 5	5 (4.54)	1 (4.34)	4 (4.6)
STAT Score, n (%)			
0.1/Category 1	13 (11.82)	3 (13.04)	10 (11.49)
0.2/Category 1	12 (10.91)	2 (8.70)	10 (11.49)
0.3/Category 2	28 (25.45)	6 (26.09)	22 (25.29)
0.4/Category 2	13 (11.82)	3 (13.04)	10 (11.49)
0.5/Category 3	1 (0.91)	0 (0)	1 (1.15)
0.6/Category 3	1 (0.91)	0 (0)	1 (1.15)
0.7/Category 3	3 (2.73)	0 (0)	3 (3.45)
0.9/Category 3	9 (8.18)	2 (8.70)	7 (8.05)
1.0/Category 4	2 (1.82)	0 (0)	2 (2.30)
1.1/Category 4	3 (2.73)	0 (0)	3 (3.45)
1.2/Category 4	14 (12.73)	5 (21.74)	9 (10.34)
1.3/Category 4	5 (4.55)	0 (0)	5 (5.75)
1.4/Category 4	1 (0.91)	1 (4.35)	0 (0)
2.1/Category 5	2 (1.82)	0 (0)	2 (2.30)
3.0/Category 5	3 (2.73)	1 (4.35)	2 (2.30)
Type of Surgery, n (%)			
Corrective	78 (70.91)	16 (69.57)	62 (71.26)
Palliative	32 (23.09)	7 (30.43)	25 (28.74)
Pre-Surgical Ventilatory Status, n (%)			
Orotracheal Intubation	75 (68.18)	5 (65.22)	60 (68.97)
Oxygen Therapy	16 (14.55)	4 (17.39)	12 (13.79)
Room Air	14 (12.72)	3 (13.04)	11 (12.64)
NIV	5 (4.55)	1 (4.35)	4 (4.60)
Immediate Postoperative Ventilatory Status, n (%)			
Orotracheal Intubation	104 (94.54)	22 (95.65)	82 (94.25)
Oxygen Therapy	4 (3.64)	1 (4.35)	3 (3.45)
NIV	2 (1.82)	0 (0)	2 (2.30)
MV Duration (days)*, Mean±SD (median)	11.46±16.07 (7)	17.65±27.46 (7)	9.82±11.02 (7)
Open Chest, n (%)	34 (30.91)	7 (30.43)	27 (31.03)
ECMO, n (%)	1 (0.91)	0 (0)	1 (1.15)
Diaphragmatic Paralysis	8 (7.27)	3 (13.04)	5 (5.75)
Post-Extubation Ventilatory Status, n (%)			
Oxygen Therapy	12 (10.91)	4 (17.39)	8 (9.20)
Room Air	10 (9.09)	3 (13.04)	7 (8.05)
NIV	88 (80)	16 (69.57)	72 (82.76)

Table 2. Study patients' characteristics (Cont.)

Variable	Total (n=110)	NIV Failure (n=23)	No NIV Failure (n=87)
NIV Modality, n (%)			
CPAP	52 (47.27)	14 (60.87)	38 (43.68)
Bilevel	58 (52.73)	9 (39.13)	49 (56.32)
NIV Duration (days)*, Mean±SD (median)	5.21±5.79 (3)	7.82±8.35 (4)	4.51±4.72 (3)
ICU Length of Stay (days)*, Mean±SD (median)	22.65±21.54 (16)	33.61±30.95 (26)	19.76±17.4 (16)
Hospital Outcome, n (%)			
ICU	2 (1.82)	0 (0)	2 (2.30)
Discharge to Ward	89 (80.91)	20 (86.96)	69 (79.31)
Transfer to Another Hospital Unit	18 (16.36)	2 (8.70)	16 (18.39)
Death	1 (0.91)	1 (4.35)	0 (0)

ECMO: Extracorporeal Membrane Oxygenation; Kg: Kilogram; MV: Mechanical Ventilation; n: Total; NIV: Noninvasive Ventilation; SD: Standard Deviation; ICU: Intensive Care Unit; %: Percentage. *p-value <0.05.

Table 3. Logistic regression model for NIV failure

Adjusted Variables	OR	p
STAT Category 2	0.75	0.67
STAT Category 3	0.37	0.31
STAT Category 4	0.55	0.46
STAT Category 5	0.52	0.61
MV duration (days)	1.01	0.51
NIV duration (days)	1.06	0.22
ICU length of stay (days)	1.01	0.64

ICU: Intensive Care Unit; MV: Mechanical Ventilation; NIV: Noninvasive Ventilation; OR: Odds Ratio.

Prolonged mechanical ventilation is associated with several complications, including pneumonia, ventilator-induced lung injury, diaphragmatic dysfunction, and generalized muscle weakness, all of which can hinder extubation and recovery.[31] Sedation and immobility may further delay weaning and contribute to respiratory muscle fatigue, ultimately predisposing patients to NIV failure.

NIV is widely used after pediatric cardiac surgery as a first-line or prophylactic therapy to avoid reintubation, providing positive pressure support without invasive airway instrumentation.[32] Its indications are generally classified as prophylactic—initiated immediately after extubation to prevent respiratory failure—or therapeutic, when applied in response to clinical signs of respiratory distress.[13] In high-risk postoperative populations, NIV use requires caution and close monitoring.[33]

Recent clinical studies comparing prophylactic versus therapeutic NIV in pediatric cardiac postoperative care indicate that prophylactic NIV may reduce the incidence of postoperative pulmonary complications (PPCs), particularly atelectasis, compared to usual care or conventional oxygen therapy. However, the evidence for reduction in reintubation rates or mortality remains of low-certainty and inconsistent across studies.

A 2023 network meta-analysis of randomized controlled trials found that prophylactic NIV after pediatric cardiac surgery significantly reduced PPCs (relative risk [RR] 0.67, 95% confidence interval [CI]: 0.49–0.93) and atelectasis (RR 0.65, 95% CI: 0.45–0.93), but did not significantly reduce reintubation rates or short-term mortality compared to standard care. The certainty of evidence was low to moderate, and the benefit over other modalities (such as high-flow nasal cannula [HFNC] or CPAP) was not definitive, though NIV ranked highest for PPC prevention.[34] Similarly, a 2024 systematic review focusing on pediatric cardiac surgery patients found no clear difference in reintubation rates between HFNC, conventional oxygen therapy, and NIV modalities, with very low certainty due to small sample sizes and study heterogeneity.[35] Another meta-analysis suggested that HFNC may reduce postextubation failure compared to other NIV techniques, but the evidence is limited and not specific to prophylactic versus therapeutic use.[36]

The STAT Mortality Score and Categories, which classify surgical procedures based on empirically derived mor-

tality risk,[1] serve as valuable indicators of postoperative complexity and potential complications. In this study, prophylactic NIV was frequently initiated in patients with higher surgical complexity, aligning with findings from Fernández Lafever et al.,[13] who observed lower NIV failure rates in patients who received prophylactic NIV (16.4%) compared with those who did not (28.7%; p=0.046). Similarly, Mayordomo-Colunga et al.[37] reported higher success rates with prophylactic NIV (81%) compared with non-prophylactic use (50%; p=0.037). This may explain why no statistically significant association was found between the STAT Mortality Score and NIV failure in our results.

Furthermore, the odds ratios observed in our study (1.01 for mechanical ventilation duration and ICU stay, and 1.06 for NIV duration) indicate very weak positive associations. These values suggest only minimal increases in failure probability with longer support times, and their clinical impact is likely negligible. Nevertheless, these parameters highlight the need for careful monitoring of NIV duration and patient response. As emphasized by Ódena et al.[16] and Rolim et al.,[38] prolonged NIV without improvement should prompt reevaluation and timely reintubation, as extended ineffective support may worsen outcomes.

Limitations

The small sample size (n=110) limits the statistical power of the study and may explain the lack of significant associations despite clinically relevant trends. This limitation, along with the retrospective single-center design, introduces potential biases such as incomplete data and institutional practice variations. Additionally, NIV outcomes can depend heavily on the clinical experience of the multidisciplinary team and individual patient comorbidities.

Despite these limitations, this study contributes to the understanding of postoperative respiratory management in pediatric CHD patients by demonstrating that the STAT Mortality Score—though not directly associated with NIV failure—may still help identify patients at higher risk who could benefit from prophylactic NIV and closer monitoring.

Conclusion

Higher-risk STAT categories are typically associated with greater surgical complexity and potentially higher mortality. However, in this study, no statistically significant association was found between the STAT Mortality Score and Categories and NIV failure in children undergoing surgery for congenital heart disease.

Although mechanical ventilation duration, NIV duration, and ICU length of stay showed odds ratios of 1.01 and 1.06, these values indicate very weak positive associations with minimal clinical relevance. Each additional day of NIV or mechanical ventilation slightly increased the likelihood of failure, but the effect was negligible.

Clinically, these findings highlight that NIV failure in this population is likely influenced more by individual postoperative factors—such as hemodynamic instability or low weight—than by the surgical risk classification itself.

Nonetheless, recognizing these subtle trends may support early identification of at-risk patients and guide decisions about prophylactic NIV use and postoperative monitoring.

Future multicenter prospective studies with larger samples are recommended to validate these results and further explore the predictive utility of STAT metrics as a complementary tool in postoperative respiratory management.

Ethics Committee Approval: Ethics committee approval was obtained from Ethics Committee of National Institute of Cardiology (Approval Number: 68156623.5.0000.5272, Date: 31.03.2023).

Informed Consent: Written informed consent was not required due to the retrospective nature of this study.

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Diagnostic Accuracy of Dynamic Ultrasound Indices for Fluid Responsiveness Using Bioreactance as the Reference Method in Shock Patients

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Abstract

Aim: Predicting fluid responsiveness in patients with shock is critical. This study aimed to evaluate the diagnostic accuracy of dynamic ultrasound-derived indices in predicting fluid responsiveness, using bioreactance-based cardiac output monitoring as the reference standard.

Study Design: A total of 39 adult patients diagnosed with shock who were receiving mechanical ventilation were included. Hemodynamic parameters were assessed using ultrasound [left ventricular outflow velocity-time integral (LVOT-VTI), respirophasic variability of LVOT-VTI, corrected carotid flow time (cCFT), respirophasic variability of carotid artery peak flow velocity (ΔVpeak), and the inferior vena cava distensibility index (dIVC)] and pulse pressure variation (PPV) via invasive arterial monitoring. The bioreactance-derived stroke volume index change after passive leg elevation (ΔSVI ≥10%) served as the reference standard for fluid responsiveness.

Results: Fluid responsiveness was present in 53.8% of patients according to ΔSVI. LVOT-VTI variability (area under the curve [AUC] 0.847, 95% confidence interval [CI]: 0.726–0.968, sensitivity 85.0%, specificity 66.6%) and PPV (AUC 0.832, 95% CI: 0.679–0.985, sensitivity 94.4%, specificity 70.5%) demonstrated the highest predictive accuracy. Carotid flow variability showed moderate performance (AUC 0.754), while dIVC yielded the lowest diagnostic accuracy (AUC 0.676). A strong correlation was observed between bioreactance-derived cardiac index and LVOT-VTI (r=0.835, p<0.001), whereas cCFT was not significantly correlated.

Conclusions: Left ventricular outflow velocity-time integral variability demonstrated strong diagnostic accuracy in predicting fluid responsiveness in mechanically ventilated patients with shock when confirmed using bioreactance monitoring. IVC distensibility and carotid flow variability showed limited reliability.

Keywords: Bioreactance; Fluid responsiveness; Shock; Ultrasound.

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Introduction

Hemodynamic instability is a common and rapidly changing condition that requires immediate intervention in critically ill patients experiencing shock. Effective and timely fluid resuscitation plays a pivotal role in restoring tissue perfusion and improving cardiac output (CO), both of which are essential for op-

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timizing patient outcomes in the intensive care setting.[1] However, the hemodynamic response to fluid loading can vary widely among patients. While some may experience a beneficial increase in cardiac output, others may not respond significantly, rendering fluid administration ineffective. In addition, unnecessary or excessive fluid administration carries significant risks, including pulmonary edema, tissue edema, intra-abdominal hypertension, and longer stays in the intensive care unit (ICU). Therefore, the ability to accurately predict fluid responsiveness is essential for optimizing patient management and minimizing iatrogenic complications.[2]

Invasive hemodynamic monitoring methods, such as pulmonary artery catheterization and transpulmonary thermodilution, have traditionally served as the gold standard for volume assessment. However, their complexity, risk of complications, and limited accessibility have led to growing interest in less invasive, bedside alternatives.[3] Among these, thoracic bioreactance and point-of-care ultrasound (POCUS) have emerged as two valuable techniques for evaluating fluid responsiveness in critically ill patients.[4]

Thoracic bioreactance, a refinement of bioimpedance technology, measures phase shifts in oscillating electrical currents as they traverse the thorax, thereby estimating cardiac output.[5,6] The clinically validated bioreactance monitor offers continuous, noninvasive measurement of key hemodynamic variables, including CO, stroke volume index (SVI), and total peripheral resistance (TPR). Notably, it allows for dynamic assessment of fluid responsiveness by calculating changes in SVI in response to the passive leg raising (PLR) maneuver, which simulates a reversible autotransfusion of approximately 300 mL of venous blood.[7-9]

Simultaneously, dynamic indices derived from bedside ultrasonography, particularly left ventricular outflow tract velocity-time integral (LVOT-VTI), corrected carotid flow time (cCFT), and inferior vena cava distensibility (IVCd), have shown considerable promise as reliable predictors of fluid responsiveness.[10-12]

In addition to baseline measurements, respirophasic variability in these ultrasound-derived indices has emerged as a valuable dynamic marker. Higher respiratory variability typically indicates fluid responsiveness, particularly when the threshold exceeds clinically validated cut-off values.[13] However, there are limited studies in the literature directly comparing the diagnostic accuracy of POCUS-based parameters with bioreactance-based monitoring.[14] In critical care settings where invasive methods are risky or impractical, such comparative analyses can facilitate clinical decision-making and improve patient safety. This study investigated the comparative diagnostic reliability of ultrasound-based dynamic indices and bioreactance measurements in determining fluid responsiveness in patients with shock.

Materials and Methods

Study Population

This observational study was conducted in the Respiratory Intensive Care Units at Trakya University Faculty of Medicine from March 2023 to April 2025. It included adult patients aged 18 to 90 years who were intubated, sedated, and mechanically ventilated with a tidal volume of at least 7 mL/kg of predicted body weight, using volume-controlled ventilation and a positive end-expiratory pressure (PEEP) of 5 cmH2O. All patients were under deep sedation with continuous intravenous infusion of midazolam and/or propofol, targeting a Richmond Agitation-Sedation Scale (RASS) score of -4 to -5. No neuromuscular blocking agents were administered. Spontaneous respiratory efforts were absent during measurements, as confirmed by clinical assessment and ventilator waveform monitoring. Patients had no arrhythmias and displayed signs of hypoperfusion, including hypotension, tachycardia, decreased skin turgor and tone, mottled skin, a capillary refill time exceeding 2 seconds, confusion, low urine output, or lactate levels above 2 mmol/L. All patients had been diagnosed with shock upon ICU admission. The definitions and standard treatment protocols for septic shock followed the guidelines of the 2016 European Society of Intensive Care Medicine and the Society of Critical Care Medicine.[15]

Patients with arrhythmias, significant valvular heart disease, poor acoustic windows, or contraindications to PLR (e.g., lower limb trauma or surgery, deep venous thrombosis, spinal or pelvic instability, intracranial hypertension) were excluded.

Hemodynamic Monitoring and Ultrasonographic Assessment

All hemodynamic and ultrasonographic measurements were conducted by a single experienced sonographer with expertise in critical care ultrasonography to minimize inter-observer variability, following a standardized sequence. These measurements were taken within

the first 24 hours of ICU admission, after hemodynamic stabilization with titration of vasoactive drugs and before fluid resuscitation. First, pulse pressure variation (PPV) was measured using an invasive arterial catheter connected to a bedside monitor [Mindray BeneView T8 monitor systems (Mindray©, Shenzhen Mindray Bio-Medical Electronics Co., Ltd., China)] with continuous waveform analysis. The monitor's software automatically calculated PPV as: $(PP_{max} - PP_{min}) / PP_{mean}$. Ultrasound-based assessments were performed next, using a Sonosite Edge II Portable Ultrasound System (FUJIFILM Sonosite Inc., Bothell, WA, USA) equipped with phased-array (1–5 MHz), linear (5–12 MHz), and curvilinear (2–5 MHz) transducers. Sequentially, the inferior vena cava (IVC) distensibility index (dIVC), LVOT-VTI and its respirophasic variability, cardiac index (CI), cCFT, and the respirophasic variability of carotid peak flow velocity (ΔV_{peak}) were measured using ultrasonography. All measurements were completed within 10–15 minutes.

dIVC: IVC measurements were obtained using a subxiphoid approach in the longitudinal plane with a phased-array transducer (2–5 MHz). The maximum (IVCmax) and minimum (IVCmin) diameters of the IVC during the respiratory cycle were measured approximately 2 cm caudal to the right atrium. The distensibility index was calculated using the following formula:

$$dIVC = [(IVC_{max} - IVC_{min}) / (IVC_{min})] \times 100$$

LVOT-VTI and LVOT-VTI respirophasic variability: LVOT-VTI was measured using pulsed-wave Doppler in the apical five-chamber view. The sample gate was placed just proximal to the aortic valve in the LVOT. Three consecutive respiratory cycles were recorded, and the average velocity–time integral (VTI) was calculated. Respiratory variation in LVOT-VTI was determined by identifying the maximum and minimum values over a full respiratory cycle. LVOT-VTI variability was calculated using the following formula:

$$\text{LVOT-VTI variability}\,(\%) = [(VTI_{max} - VTI_{min})] / [(VTI_{max} + VTI_{min}) / 2] \times 100$$

Cardiac index: Cardiac output was calculated as:

$$CO = VTI \times LVOT\ Area \times HR$$

where the LVOT area was derived from the LVOT diameter (D) measured in the parasternal long-axis view [LVOT Area = $\pi \times (D/2)^2$]. CI was then obtained by normalizing CO to the body surface area.

cCFT and ΔV_{peak}: The corrected carotid flow time was measured on the right common carotid artery using pulsed-wave Doppler, with the sample volume positioned in the mid-segment of the artery and the patient in a supine position. The raw carotid flow time (CFT) was obtained from the onset of the systolic upstroke to the dicrotic notch on the Doppler waveform. The cCFT was calculated using Wodey's formula:[16]

$$cCFT = CFT + 1.29 \times (HR - 60)$$

The maximum carotid flow velocities (V_{peak}) during inspiration and expiration were recorded, and the respiratory variation was expressed as:

$$\Delta V_{peak}\,(\%) = (Vpeaki_{nsp} - Vpeak_{exp}) / [(Vpeaki_{nsp} + Vpeak_{exp})/2] \times 100$$

After ultrasound-based measurements, the Starling™ bioreactance-based noninvasive cardiac output monitor (Cheetah Medical, USA) was used to obtain bioreactance-based hemodynamic measurements for comparison.

CI and ΔSVI with the bioreactance method: The Starling™ monitor was connected to the patient, and CI was measured using the bioreactance method. The patient started in a head-up, 45° semi-recumbent position for the PLR maneuver. Then, their legs were passively raised to 45° while the upper body was lowered to a horizontal supine position. SVI was recorded before and between 30 and 90 seconds after PLR, with the monitor's software calculating the percentage change in SVI (ΔSVI) as:

$$\Delta SVI\,(\%) = [(SVI_{post\text{-}PLR} - SVI_{baseline}) / SVI_{baseline}] \times 100$$

Data Collection

The patient's sex, age, Charlson Comorbidity score, Acute Physiology and Chronic Health Evaluation (APACHE II) score, and Sequential Organ Failure Assessment (SOFA) score at ICU admission were recorded. The dIVC, LVOT-VTI, CI, respirophasic variability of LVOT-VTI, cCFT, and ΔV_{peak} were measured using sonography and recorded, while PPV, CI, total peripheral resistance, and ΔSVI with PLR were measured and recorded using a bioreactance monitor. Shock types were determined by the primary physician based on clinical characteristics and bioreactance monitor results (CI, TPR). Fluid responsiveness was defined as ΔSVI ≥10%, following established hemodynamic criteria. ICU length of stay (LOS) and patient outcomes were also recorded.

Statistical Analysis

Categorical variables are presented as frequencies and proportions (n, %), whereas continuous variables are reported as median [25th–75th percentile]. Fisher's exact test was used for categorical data, but, and the Mann-Whitney U test was used for numerical variables. Cronbach's alpha reliability, specificity, sensitivity, and kappa measures of agreement were computed for dIVC, CF variability, LVOT-VTI variability, and PPV compared with ΔSVI, and for CI assessed by ultrasonography and cCFT compared with CI recorded by the bioreactance monitor. Cohen's kappa coefficient was calculated to evaluate the categorization agreement between the two distinct approaches. The degree of agreement among the methodologies was categorized and statistically assessed using kappa values. Internal consistency of the methods was assessed using Cronbach's Alpha coefficient. To evaluate their ability to determine volume responsiveness compared to ΔSVI, correlation analyses and receiver operating characteristic (ROC) curve area under the curve (AUC) analyses were performed for dIVC, CF variability, LVOT-VTI variability, and PPV. Two-tailed analyses were used, and 95% confidence intervals (CI) were calculated. A P-value of less than 0.05 was deemed statistically significant. Established cut-off values of dIVC (18%), ΔV_{peak} (12%), LVOT-VTI variability (20%), and PPV (12%) for evaluating fluid responsiveness were used. The method described by DeLong et al.[17] was used for comparison of the ROC curves. Data management and analyses were performed using the statistical software SPSS (IBM® SPSS® Statistics v25, IL, USA, 2017).

Ethical Aspects

The study was approved by Trakya University Non-Interventional Scientific Research Ethics Committee (Protocol Number: TÜTF-GOBAEK 2025/276, Approval Number: 12/14, Date: 07.07.2025). The study was conducted in compliance with the 2008 Declaration of Helsinki. In accordance with the clinic's regulatory protocols, patients or their legally authorized family members provided written informed consent at admission for the processing and publication of their medical records for scientific purposes.

Results

A total of 39 patients who met the inclusion criteria were enrolled in the study. The median age of the cohort was 70 years [60–77], and 51.3% (n=20) were male. The median APACHE II score at ICU admission was 29.5 [22.7–33.2], corresponding to a predicted mortality rate (APACHE PMR) of 67.2% [47.8–83.0]. The median SOFA score was 12 [11–13], indicating high baseline illness severity (Table 1).

Baseline hemodynamic characteristics obtained from invasive arterial monitoring revealed a median heart rate of 98 [74–116], a median mean arterial pressure of 70 [63–78], and a PPV of 13% [8%–17%]. Eighteen (51.4%) patients had a PPV value of 12 or above. Among ultrasound-derived parameters, CI measured via LVOT-VTI Doppler was 3.6 [2.6–4.1] L/min/m², and cCFT was 317.9 [278.5–358.6] ms. The median IVC distensibility index was 17% [12%–28%], LVOT-VTI variability was 23% [18%–26%], and carotid flow ΔV_{peak} was 14% [11%–21%]. Based on dIVC, 21 (53.8%) patients were classified as fluid responsive, while 20 (52.63%) were classified as responsive according to LVOT-VTI variability and ΔV_{peak};

Table 1. Patient characteristics, severity scores, hemodynamic measurements at the time of Intensive Care Unit admission, and outcomes

Characteristics	N=39
Age (years)	70 [60–77]
Gender, male*	20 (51.3)
Charlson Comorbidity Index	5 [3–7]
APACHE II	29.5 [22.7–33.2]
SOFA	12 [11–13]
IVC distensibility	17 [12–28]
CI (LVOT-VTI) (L/min/m²)	3.6 [2.6–4.1]
LVOT-VTI variability	23 [18–26]
cCFT (ms)	317.9 [278.5–358.6]
ΔV_{peak}	14 [11–21]
PPV	13 [8–17]
CI (bioreactance) (L/min/m²)	3.4 [2.5–4.1]
TPR (dyn·s/cm⁵)	984 [858–1216]
ΔSVI with PLR	11 [4–16]
Shock type*	
Distributive	26 (66.7)
Hypovolemic	9 (23.1)
Cardiogenic	2 (5.1)
Obstructive	2 (5.1)
ICU LOS	14 [7–26]
Hospital LOS	29 [7–45]
28-day mortality*	19 (48.7)

APACHE II: Acute Physiology and Chronic Health Evaluation; SOFA: Sequential Organ Failure Assessment; IVC: Inferior vena cava; CI: Cardiac index; LVOT-VTI: Left ventricular outflow tract velocity time integral; cCFT: Corrected carotid flow time; ΔVpeak: Carotid flow peak velocity respirophasic variability; PPV: Pulse pressure variation; TPR: Total peripheral resistance; ICU: Intensive care unit; LOS: Length of stay. Data expressed as median [25th-75th percentile]. *n (%).

and according to ΔV_{peak} alone, 18 (56.2%) patients. In the bioreactance-based measurements, CI was 3.4 L/min/m² [2.5–4.1], TPR was 984 dyn·s/cm⁵ [858–1216], and the PLR-induced ΔSVI was 11% [4–16]. The distribution of shock types, according to the monitor's measurements, was as follows: distributive shock in 26 patients (66.7%), hypovolemic shock in nine patients (23.1%), cardiogenic shock in two patients (5.1%), and obstructive shock in two patients (5.1%). Based on the bioreactance-derived ΔSVI with PLR, 53.8% (n=21) of patients were classified as volume responsive (Table 1).

A strong correlation was observed between CI measurements obtained using LVOT-VTI and those obtained using the monitor, with a Spearman's rank correlation coefficient of 0.835 (p<0.001). However, no significant correlation was found between CI measured by the monitor and cCFT, with a Spearman's rank correlation coefficient of 0.156 (p=0.395). The sensitivity and specificity values for predicting volume responsiveness were highest for PPV, with a sensitivity of 94.4% and a specificity of 70.5%. LVOT-VTI variability also demonstrated high sensitivity (85.0%) but slightly lower specificity (66.6%). Kappa measures of agreement were 0.538 for PPV and 0.463 for LVOT-VTI variability (p=0.01 and p=0.003, respectively). Cronbach's alpha indicated the highest internal consistency for PPV (0.728), followed by LVOT-VTI variability (0.656), ΔV_{peak} (0.568), and IVC distensibility (0.559) (Table 2). LVOT-VTI variability and PPV demonstrated the highest predictive ability for volume responsiveness, with AUC values of 0.847 (95% confidence interval [CI]: 0.726–0.968, p<0.001) and 0.832 (95% CI: 0.679–0.985, p=0.001), respectively. CF variability showed moderate correlation (r=0.36, p=0.03) with an AUC of 0.754 (95% CI: 0.587–0.921, p=0.01), while IVC distensibility demonstrated weaker correlation (r=0.21, p=0.20) with a lower AUC of 0.676 (95% CI: 0.495–0.857, p=0.06) (Table 3, Fig. 1). There was no difference in the pairwise comparisons of the ROC curves for PPV, LVOT-VTI variability, ΔV_{peak}, or dIVC in predicting fluid responsiveness (Supplementary Table 1). ICU mortality was 48.7% (n=19), and the standardized mortality ratio (SMR) was calculated as 72.4%. Median ICU LOS was 14 [7–26] days, and median hospital LOS was 29 [interquartile range [IQR]: 7–45] days.

Table 2. Specificity, sensitivity, agreement, and reliability of inferior vena cava distensibility, carotid flow variation, left ventricular outflow tract velocity-time integral variability, and pulse pressure variation in discriminating volume responsiveness compared to the stroke volume index change during passive leg raising

	Cut-off	Specificity	Sensitivity	Kappa measure of agreement	p	Cronbach's Alpha
IVC distensibility	18%	72.2	66.6	0.386	0.015	0.559
ΔV_{peak}	12%	78.5	61.1	0.385	0.02	0.568
LVOT-VTI variability	20%	66.6	85	0.463	0.003	0.656
PPV	12%	70.6	94.4	0.538	0.01	0.728

IVC: Inferior vena cava; ΔVpeak: Carotid flow peak velocity respirophasic variation; LVOT-VTI: Left ventricular outflow tract velocity time integral; PPV: Pulse pressure variation.

Table 3. Correlation and receiver operating characteristic–area under the curve (ROC-AUC) analysis of inferior vena cava distensibility, carotid flow variability, left ventricular outflow tract velocity–time integral (LVOT-VTI) variability, and pulse pressure variation for assessing volume responsiveness determined by stroke volume change during passive leg raising

	Correlation		ROC		
	r	p	AUC	95% CI	p
IVC distensibility	0.21	0.20	0.676	0.495–0.857	0.06
ΔVpeak	0.36	0.03	0.754	0.587–0.921	0.01
LVOT-VTI variability	0.46	0.003	0.847	0.726–0.968	<0.001
PPV	0.44	0.008	0.832	0.679–0.985	0.001

ROC-AUC: Receiver operating characteristic – area under the curve; IVC: Inferior vena cava; ΔVpeak: Carotid flow peak velocity respirophasic variation; LVOT-VTI: Left ventricular outflow tract velocity time integral; PPV: Pulse pressure variation.

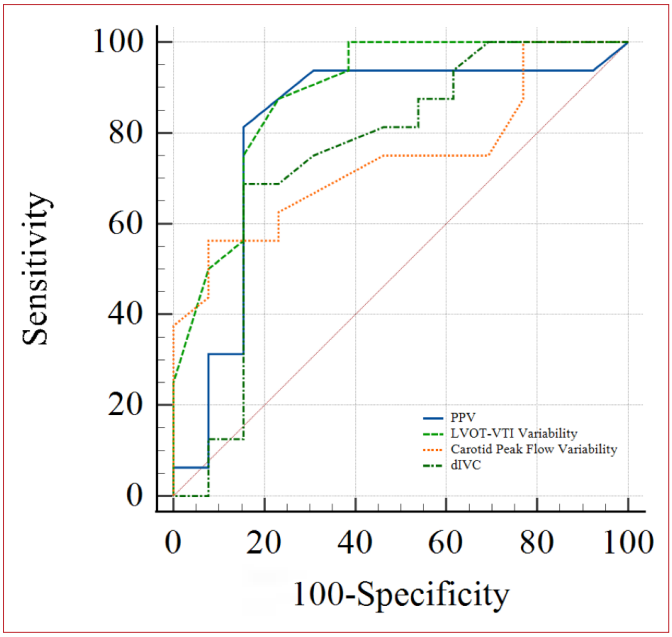

Figure 1. Receiver operating characteristic curve analysis for predicting fluid responsiveness.

Discussion

In this observational study, we investigated the comparative diagnostic performance of ultrasound-based dynamic indices for assessing fluid responsiveness in mechanically ventilated patients with shock, using bioreactance-based noninvasive CO monitoring measurements. Our findings indicate that LVOT-VTI respirophasic variability and PPV parameters exhibit high sensitivity, specificity, and predictive value compared to the ΔSVI reference standard obtained via PLR. LVOT-VTI variability demonstrated the highest accuracy among all ultrasound parameters in terms of AUC value (AUC=0.847), while PPV showed the highest sensitivity (94.4%). In contrast, the correlation coefficients and AUC values of dIVC and ΔV_{peak} measurements were lower in predicting fluid responsiveness compared to the bioreactance-based SVI change during PLR.

In intensive care practice, fluid therapy has long been based on "static" cardiac preload indices such as central venous pressure. However, static parameters (central venous pressure, pulmonary artery occlusion pressure, E/e' ratio on echocardiography, left ventricular end-diastolic surface/volume, or global end-diastolic volume) are insufficient for predicting the effectiveness of fluid loading.[18,19] The main reason for this is that the slope of the Frank–Starling curve varies from patient to patient, and the same preload level may lead to a responsive state in some patients but not in others. For this reason, "dynamic" approaches have come to the fore in fluid therapy decisions rather than static measurements. Dynamic indices and tests enable the determination of preload responsiveness by observing changes in stroke volume, cardiac output, or their surrogate parameters during controlled or spontaneous alterations in cardiac preload. As a result of the cardiopulmonary interactions of positive-pressure mechanical ventilation, changes in intrathoracic pressure cyclically affect ventricular filling and emptying conditions, leading to predictable stroke volume changes during inspiration and expiration in preload-sensitive patients. The superiority of this physiologically based dynamic approach over static methods has been conclusively demonstrated, and considering the potential side effects of fluid therapy, it is recommended that preload responsiveness be assessed using these methods prior to treatment.[20] Among dynamic indices, PPV reflects stroke volume variability by measuring the change in systolic–diastolic pressure difference throughout the respiratory cycle and is one of the parameters with the highest level of evidence for predicting fluid responsiveness in mechanically ventilated patients.[21,22] A cut-off value of 12% is generally accepted. In the absence of invasive arterial monitoring, the respiratory variation in LVOT-VTI measured by echocardiography can also be used to assess preload responsiveness.

The findings of our current study demonstrate that respiratory variation in LVOT-VTI and PPV have significant diagnostic value in predicting fluid responsiveness. These results partially align with data obtained by Xie et al.[23] in critically ill postoperative patients who were mechanically ventilated with low tidal volumes (<8 mL/kg). In the study by Xie et al.,[23] variation in LVOT-VTI showed the highest predictive value, with an AUC of 0.919, 78.1% sensitivity, and 96.4% specificity, while PPV demonstrated moderate accuracy with an AUC of 0.797. In our study, however, LVOT-VTI variability emerged as a key indicator, with an AUC of 0.847, 85% sensitivity, and 66.6% specificity. PPV achieved the highest sensitivity at 94.4%, with an AUC of 0.832. Correlation analyses revealed a moderate relationship between LVOT-VTI variability and bioreactance-based ΔSVI (r=0.46, p=0.003). In contrast, the correlation coefficient between PPV and ΔSVI was higher, indicating that PPV is a relatively stronger parameter for determining fluid responsiveness. In the study by Xie et al.,[23] a very

strong correlation (r=0.798, p<0.001) was reported between LVOT-VTI variation and stroke volume change after PLR, along with a high correlation (r=0.704, p<0.001) with PPV. This discrepancy may arise from differences in patient populations and ventilation parameters, as well as methodological differences in reference measures. In our study, bioreactance-based ΔSVI was used as the reference standard, relying on technology that eliminates operator dependence and provides continuous, objective measurements. Conversely, Xie et al.'s study[23] defined fluid responsiveness based on stroke volume changes measured via transthoracic echocardiography, a method that is highly dependent on the sonographer's experience and image quality. Therefore, the use of a more objective and reproducible reference method in our study may have contributed to findings that were less susceptible to measurement bias. Feissel et al.[24] investigated ΔV_{peak} measured with transesophageal echocardiography as a predictor of fluid responsiveness in septic shock patients, using fluid bolus administration as the reference method and defining responsiveness by an increase in CI after volume expansion. They reported that a 12% ΔV_{peak} threshold yielded 100% sensitivity and 89% specificity, with a very strong linear correlation between baseline ΔV_{peak} and fluid-induced CI change (r^2=0.83; p<0.001). The superior performance observed in Feissel et al.'s study[24] may be attributed to differences in the measurement techniques used (transthoracic versus transesophageal echocardiography), reference standards (fluid bolus versus PLR), and variations in patient characteristics and technical factors. Nevertheless, across studies, dynamic indices based on respiratory variations in LVOT or large-vessel blood flow velocities consistently emerge as strong and clinically applicable predictors of fluid responsiveness in appropriately selected patients.

Although LVOT-VTI variation measured by transthoracic or transesophageal echocardiography is highly reliable for determining fluid responsiveness, it requires high-quality images from specific windows, and the process is highly operator-dependent because it demands advanced echocardiographic expertise.[25] Especially in emergency and intensive care settings, the patient's position, lung pathology, or chest wall anatomy can negatively affect image quality. In contrast, measurements based on carotid artery ultrasound (cCFT and ΔV_{peak}) are easier to learn, can be performed quickly via neck access, and are relatively less operator-dependent. Although these methods do not provide as much central hemodynamic information as LVOT-VTI, they stand out as noninvasive and practical alternatives when LVOT-VTI measurement is impractical. Thus, they can contribute to the rapid and repeatable assessment of fluid responsiveness in critically ill patients. The meta-analysis by Singla et al.[11] evaluated the clinical value of several predictive parameters in patients undergoing elective surgery with general anesthesia and mechanical ventilation. The analysis included 10 studies that examined the predictive power of cCFT and ΔV_{peak} parameters for fluid responsiveness. The overall sensitivity for cCFT was 75.8%, while the overall specificity was 88.3%, indicating moderate to low heterogeneity. The summary ROC curve demonstrated an AUC of 0.909, with a Q value of 0.841. For ΔV_{peak}, heterogeneity ranged from absent to moderate, yielding a pooled sensitivity of 82.8% and a pooled specificity of 80.5% (95% CI: 73.6%–86.4%). In our study, the correlation coefficients and AUC values for ΔV_{peak} were lower compared to bioreactance-based changes in SVI. This may be related to differences within the patient population, the reference methods used, and the impact of technical factors on the results. Various technical errors that could affect the reliability of carotid Doppler-based measurements may be present, including minor changes in the insonation angle of the ultrasound probe, causing disproportionate errors in velocity measurement; variability in vessel diameter depending on the cardiac cycle or respiratory phase; probe pressure partially compressing the arterial lumen and affecting flow velocity; and other anatomical structures interfering with image quality during measurement.[26] The fact that our study was conducted in intensive care conditions, on hemodynamically unstable patients with limited mobility, may have accentuated the effects of these technical limitations. Therefore, the relatively low correlation and AUC values obtained should be viewed as reflecting the combined influence of both the patient population and technical factors.

Inferior vena cava ultrasonography is one of the most widely used and applied methods for estimating fluid responsiveness. As intrathoracic pressure fluctuates throughout the respiratory cycle, a cyclical change in venous return occurs, resulting in changes in IVC diameter.[27] Respirophasic changes in IVC diameter have been studied in both mechanically ventilated and spontaneously breathing patients. Because the minimum and maximum values of intrathoracic pressure during spontaneous breathing and mechanical ventilation differ

across the respiratory cycle, the use of the IVC collapsibility index is necessary in spontaneously breathing patients,[28] whereas the distensibility index is necessary under mechanical ventilation.[27] However, this variability can be influenced by many factors in both spontaneously breathing and mechanically ventilated patients and can be misleading when estimating fluid responsiveness.[29] Factors that decrease venous return (tricuspid insufficiency, tamponade, pulmonary hypertension, etc.) or increase intra-abdominal pressure affect IVC size regardless of fluid status.[30,31] In addition, variations in inspiratory effort in spontaneously breathing patients affect measurement accuracy.[32] While better diagnostic performance is generally observed in mechanically ventilated patients without spontaneous breathing,[33,34] settings such as high PEEP[35,36] and low tidal volume may affect variability.[37] Many meta-analyses have yielded different results regarding the diagnostic performance of the dIVC index in predicting fluid responsiveness.[12,33,34,37] However, these studies agree on the heterogeneity of the patient populations examined, which may explain the conflicting results. In a recent meta-analysis of 15 studies evaluating the diagnostic performance of the dIVC index for assessing fluid responsiveness in sepsis patients, the sensitivity and specificity of dIVC were reported as 0.79 (95% CI: 0.68–0.86) and 0.82 (95% CI: 0.73–0.89), respectively; the diagnostic odds ratio was 17.1 (8.1–36.0), and the AUC was 0.88 (95% CI: 0.84–0.90).[38] In our study, the correlation of dIVC with the reference method was weak, and its diagnostic performance was lower than that reported in other studies. In our study, measurements were taken while patients without spontaneous breathing were ventilated with an invasive mechanical ventilator, a tidal volume of 7 mL/kg or higher, and a fixed PEEP value. Although the cause of shock was mostly sepsis, other shock types were also included, which may explain the differences in our results.

This study has several limitations that should be acknowledged. First, the relatively small sample size from a single center limits the generalizability of the findings to broader critically ill populations. Second, the study population included patients with different shock etiologies, which may have introduced heterogeneity in hemodynamic responses. This clinical diversity could influence the diagnostic performance of dynamic ultrasound indices and potentially limit the generalizability of our findings to more homogeneous patient groups.

Third, although a single experienced operator performed ultrasonographic measurements to minimize inter-observer variability, this design prevents the evaluation of reproducibility and inter-operator reliability. Fourth, the inclusion criteria were limited to patients under controlled mechanical ventilation without spontaneous breathing and with fixed ventilatory settings (tidal volume ≥7 mL/kg, fixed PEEP), which restricts the applicability of the results to spontaneously breathing patients or those managed with protective ventilation strategies. Lastly, although bioreactance-based ΔSVI with PLR was chosen as the reference standard because of its noninvasive and reproducible nature, it is important to emphasize that it is not an absolute gold standard compared with invasive methods such as transpulmonary thermodilution, especially in cases of severe shock with poor peripheral perfusion. Under such conditions, its reliability may be compromised. In addition, two patients with obstructive shock in our cohort demonstrated echocardiographic signs of right ventricular pressure overload, including septal flattening and elevated pulmonary artery pressure. As right ventricular dysfunction may impair the transmission of preload changes to the left heart, the accuracy of PPV in these specific cases may have been affected, representing a physiological limitation worth noting.

In conclusion, this study demonstrates that the dynamic ultrasound-derived indices LVOT-VTI variability and PPV provide significant diagnostic value in predicting fluid responsiveness in mechanically ventilated patients with shock. Although dIVC and carotid flow variability showed weaker correlations with bioreactance-derived ΔSVI in our study, they can still serve as complementary tools when optimal echocardiographic windows or invasive monitoring are not available. Together, our findings suggest that physiologically based dynamic indices may serve as practical alternatives to invasive monitoring in predicting fluid responsiveness. However, these results should be interpreted as exploratory and primarily hypothesis-generating. Larger, multicenter studies in more homogeneous populations are warranted to validate these preliminary observations and enhance clinical applicability. Additionally, future studies might incorporate alternative methods, such as the mini fluid challenge, alongside PLR when using bioreactance-based monitoring, which may further improve diagnostic performance and generalizability.

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38th Annual Congress, October 25-29, 2025. The abstract was be published in the Congress proceedings book.

Ethics Committee Approval: Ethics committee approval was obtained from Trakya University Non-Interventional Scientific Research Ethics Committee (Protocol Number: TÜTF-GOBAEK 2025/276, Approval Number: 12/14, Date: 07.07.2025).

Informed Consent: In compliance with the clinic's regulatory protocols, patients or their legally permitted family members provided written informed consent at the time of admission for the processing and publication of their medical records for scientific purposes.

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Supplementary Table 1. Pairwise comparison of receiver operating characteristic (ROC) curves

Comparison	Difference	Standard Error	95% CI	z statistic	p
PPV ~ LVOT_VTI_variability	0.0721	0.0996	-0.123-0.267	0.724	0.4692
PPV ~ ΔVpeak	0.0721	0.121	-0.165-0.309	0.597	0.5503
PPV ~ dIVC	0.0649	0.125	-0.180-0.309	0.52	0.6027
LVOT_VTI_variability ~ΔVpeak	0.144	0.0823	-0.017-0.306	1.752	0.0797
LVOT_VTI_variability ~ dIVC	0.137	0.109	-0.075-0.35	1.262	0.207
ΔVpeak ~ dIVC	0.00721	0.12	-0.227-0.242	0.0602	0.952

PPV ~ LVOT_VTI: Pulse pressure variation, LVOT-VTI: Left ventricular outflow velocity-time integral, ΔVpeak: Respirophasic variability of carotid artery peak flow velocity, dIVC: Inferior vena cava distensibility index.

CASE REPORT

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West Nile Virus Encephalitis in a Kidney Transplant Patient

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Abstract

West Nile virus encephalitis is a neuroinvasive condition with significant diagnostic challenges, especially in immunosuppressed patients. We describe the case of a 54-year-old male patient with a history of kidney transplantation and systemic comorbidities. He presented with fever and altered mental status, and neuroimaging revealed bilateral thalamic lesions and leptomeningeal enhancement. West Nile virus was confirmed via polymerase chain reaction from cerebrospinal fluid. The patient was managed with supportive care and close monitoring. Early recognition and comprehensive diagnostics are crucial for effectively managing high-risk patients, despite the lack of a specific treatment for West Nile virus, as with most other viral diseases.

Keywords: Encephalitis; Kidney transplantation; Leptomeningeal involvement; West Nile virus.

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Introduction

West Nile virus (WNV), a single-stranded RNA virus belonging to the *Flaviviridae* family and classified under the *Flavivirus* genus, is primarily transmitted by mosquitoes, particularly those of the *Culex* genus. Transmission can also occur through the bite of an infected animal, and in rare cases, via blood transfusions and solid organ transplants.[1,2] The majority of WNV cases are asymptomatic or present with flu-like symptoms. WNV with neurological involvement, such as encephalitis and meningitis, can be fatal in one out of every 150 cases.[3] The West Nile virus has also been shown to induce dysfunction in the cranial nerves.

We describe a case of West Nile virus encephalitis with a comprehensive evaluation of a patient who presented with fever, altered consciousness, bilateral thalamic lesions, and pathologic contrast enhancement in the right trigeminal nerve and both oculomotor nerve cisternal segments on cranial magnetic resonance imaging. In this case, we aimed to emphasize the difficulties in identifying West Nile virus and the increased exposure to opportunistic pathogens with greater numbers of organ transplantations. Signed consent was obtained from the patient's guardian.

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Case Report

A 54-year-old male patient with a history of type 2 diabetes mellitus, hypertension, coronary artery disease, and kidney transplantation secondary to diabetic nephropathy was admitted to the emergency department with a fever of 38.3°C, decreased communication, nausea and vomiting, diarrhea, and poor oral intake. The Glasgow Coma Scale score at admission to hospital was 15. Vitals signs were: peak heart rate 96 beats/min, blood pressure 142/81 mmHg, SpO_2 97%, and respiratory rate 23/min. Although the quick Sequential Organ Failure Assessment (qSOFA) score was 1, the patient was considered to have sepsis given the clinical picture. The immunosuppressive drugs he was taking included prednisolone, tacrolimus, and mycophenolate mofetil. Mycophenolate mofetil was discontinued in consultation with the transplantation team, as the patient also had a history of kidney transplantation, and stress-dose corticosteroid methylprednisolone treatment was started.

Brain Magnetic Resonance Imaging (MRI) was performed to investigate the possibility of cerebrovascular events, given the patient's altered consciousness. A right thalamic infarction was detected on diffusion-weighted MRI (Fig. 1), and the patient was referred to Neurology. In the patient presenting with diarrhea and a history of broad-spectrum antibiotic use within the past three months, testing for *Clostridioides difficile* toxin A/B was requested to evaluate for possible antibiotic-associated enterocolitis. Cytomegalovirus (CMV) polymerase chain reaction (PCR) testing was also performed to investigate a viral etiology. CMV DNA PCR was below 500 quantitative copies, and *C. difficile* toxin A/B was negative. One day after admission to the hospital, the patient exhibited signs of somnolence. He opened his eyes in response to painful stimuli, made incomprehensible sounds, and his Glasgow Coma Scale (GCS) score dropped from 15 to 7. The patient underwent orotracheal intubation to ensure airway safety. On the second day of intensive care monitoring, a GCS of 3 was observed, and an electroencephalogram (EEG) was performed. Rare sharp-slow wave activity was observed in the left frontotemporal and occipital regions on EEG. These findings were interpreted as indicative of a tendency toward hypersynchronization in the left frontotemporal and left occipital regions based on widespread irregularity. Unconsciousness, rightward gaze deviation, eye ptosis, and absent pupillary light reflex in the left eye were observed. Therefore, contrast-enhanced brain MRI was performed, and chronic ischemic gliotic hyperintensities were observed in the cerebral white matter. The millimetric acute ischemic diffusion restriction areas defined in the previous examination at the bilateral thalamic level showed marked regression (Fig. 2). Minimal leptomeningeal contrast enhancement was observed in the cerebellar folia. Contrast enhancement was also found in the right trigeminal nerve and both oculomotor nerve cisternal segments.

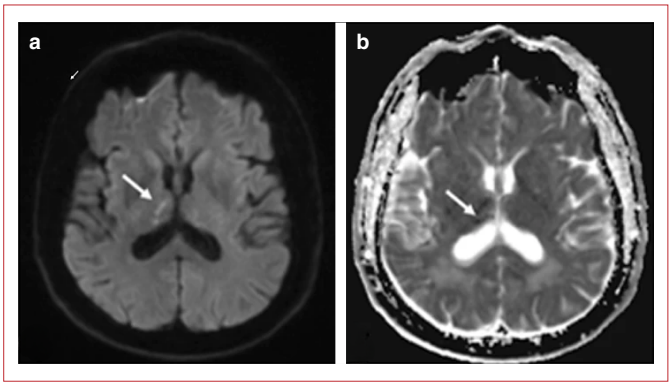

Figure 1. Diffusion-weighted magnetic resonance imaging (MRI) scan. (a) Right and left thalamic cytotoxic edema is observed as diffusion restriction in a linear pattern (arrow). (b) Apparent diffusion coefficient (ADC) maps show ADC hypointensity confirming right thalamic cytotoxic edema (arrow).

Considering the preliminary diagnosis of meningitis or leptomeningeal/perineural involvement of a systemic or neoplastic process, a lumbar puncture was performed and cerebrospinal fluid (CSF) analysis was conducted. The glucose level in the CSF was 153 mg/dL, while the simultaneous blood glucose level was 192 mg/dL, and the protein level was 169 mg/dL. CSF showed 40/μl leukocytes and 60/μl erythrocytes, comprising 80% basophils and 20% lymphocytes. Infectious Diseases and Clinical Microbiology (IDCM) consultation was requested. The meningoencephalitis panel FilmArray (BIOFIRE®) was negative. It was planned to repeat CSF sampling and investigate atypical agents (West Nile virus, *Treponema pallidum*, oligoclonal bands, CMV, *varicella zoster virus (VZV), herpes simplex virus (HSV), Toxoplasma gondii, adenovirus*), immunoglobulin G (IgG) index, beta-D-glucan, fungal culture, flow cytometry, and paraneoplastic/autoimmune encephalitis panel tests. Paraneoplastic/autoimmune encephalitis panels, ganglioside panels, and tests for *Brucella, Borrelia, and Mycobacterium tuberculosis* were also performed in blood. The PCR test for West Nile virus, performed at the Ministry of Health, yielded a positive result. Since the clinical and laboratory findings

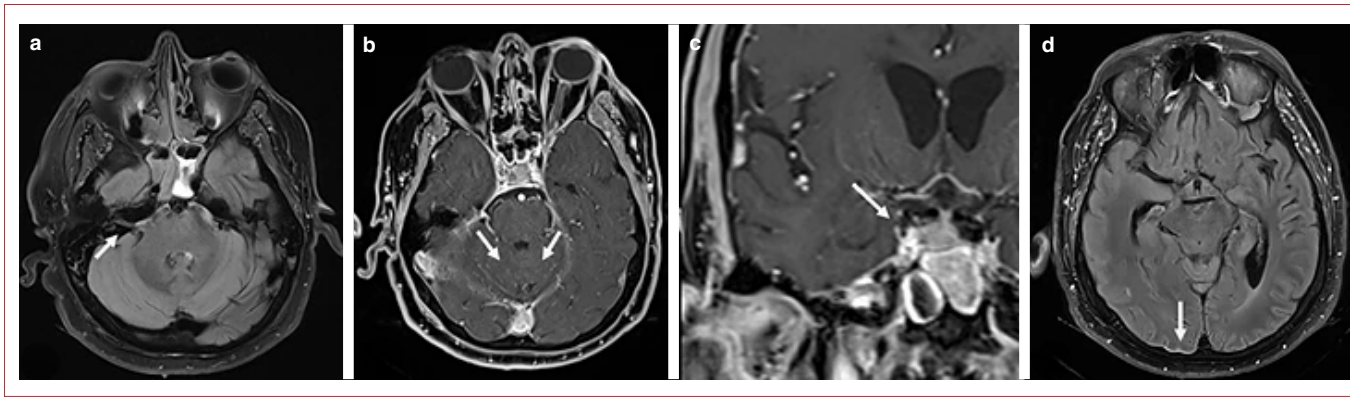

Figure 1. Postcontrast magnetic resonance imaging (MRI). (a) Post-contrast fluid-attenuated inversion recovery (FLAIR) scan shows focal perineural contrast enhancement in the right trigeminal nerve intracanalicular segment (arrow). (b) Post-contrast axial T1A series shows leptomeningeal contrast enhancement in the superior cerebellar follicles (arrow). (c) Post-contrast coronal T1A series shows contrast enhancement in the right oculomotor nerve cisternal segment (arrow). (d) Post-contrast FLAIR scan shows mild dural contrast enhancement in the right occipital convexity (arrow).

were compatible, the patient was diagnosed with West Nile virus encephalitis, and empirical antibiotic treatment was discontinued as no other agent was detected.

Discussion

In this report, we describe the clinical course, diagnostic workup, and therapeutic process of a rare case of WNV-associated encephalitis in a kidney transplant recipient. The present WNV case is among the few reported in the literature, characterized by severe neurological symptoms that necessitated admission to the intensive care unit and a permanent tracheostomy. With increasing awareness and reported case numbers, WNV is of epidemiological importance in various regions. According to European Centre for Disease Prevention and Control (ECDC) data, 1,202 cases of WNV were reported by November 2024.[4]

Immunosuppressed patients, particularly solid organ transplant (SOT) recipients, hematopoietic stem cell transplant (HSCT) recipients, and patients receiving B-cell-depleting therapies, can significantly alter the epidemiological profile of WNV transmission. Donor-derived transmission through organ or blood transfusion has been documented. Additionally, the onset of infection in transplant recipients has been reported to occur up to approximately 50 months after transplantation.[5] Our patient underwent a kidney transplant 36 months earlier, and there is a possibility of infection from the donor. There is also a possibility of WNV infection from red blood cells and fresh frozen plasma transfusions. Organ donors are not routinely screened for WNV, and both organ donors and transplant recipients often receive multiple blood transfusions. Therefore, screening both SOT donors and blood donors for WNV may allow for earlier detection of the virus.[6]

Approximately one-fifth of patients infected with WNV develop fever, headache, neck pain, and flu-like symptoms. It has been shown that neuroinvasive disease can develop in one out of every 150 to 250 cases.[7] In solid organ transplant recipients with donor-derived WNV infection, up to 75% develop neuroinvasive disease, which may present as meningitis, encephalitis, or acute flaccid paralysis.[5,8] Subsequently, neurological symptoms may manifest, including altered mental status, weakness, and abnormal movements.[5]

Neuroimaging plays an important role in the evaluation of suspected WNV encephalitis. Brain computed tomography (CT) scans are often normal in the early stages of infection; MRI has higher sensitivity in detecting inflammatory changes in the brain parenchyma. Characteristic MRI findings include T2-weighted hyperintensities and diffusion restrictions in regions such as the thalamus, basal ganglia, brainstem, and white matter, though these findings are not always present. Leptomeningeal contrast enhancement may also be observed, indicating more widespread meningeal involvement.[8] Our patient had T2-weighted hyperintense areas in the white matter and leptomeningeal contrast enhancement.

For diagnostic confirmation, if there is a clinical suspicion or detailed patient history suggesting the possibility of WNV infection, the Centers for Disease Control and Prevention (CDC) guidelines recommend a more nuanced approach: if neurological symptoms are present,

PCR testing on CSF should be considered as an initial diagnostic tool. In cases of PCR positivity, the diagnosis is considered confirmed, and the patient should be managed accordingly. Conversely, in cases where only serological testing (immunoglobulin M, IgM positivity) is observed, the patient should be treated as a suspected case, and further monitoring is required.[1,9]

Like most viral infections, there is no specific antiviral treatment for WNV; patients are typically given symptomatic and supportive care. In selected cases, reduction of immunosuppressive therapy has been associated with clinical improvement. Despite interventions, a 30% mortality rate has been reported in patients with severe encephalitis who have undergone kidney transplantation with neuroinvasive WNV. Survivors of WNV encephalitis may experience long-term neurological sequelae, including cognitive impairment, motor deficits, and neuropsychiatric disorders, all of which contribute to a decline in quality of life.[10-12]

In light of current data and considering the high morbidity and mortality associated with WNV encephalitis in kidney transplant patients, preventive measures are of great importance. Although routine screening of organ donors for WNV is not mandatory in all regions, targeted screening is recommended in endemic areas or during periods of high WNV activity.[11,13]

Conclusion

West Nile virus infection has been shown to cause meningoencephalitis. Patients who have undergone kidney transplantation are at higher risk due to immunosuppressive therapy. Especially in endemic areas, advanced donor screening is a critical measure that can reduce the incidence of WNV transmission from donors. Early diagnosis and prompt supportive treatment are crucial for optimizing patient outcomes. Therefore, the education of organ transplant surgeons and infectious disease specialists is important. Further clinical studies are needed to better understand the disease and optimize treatment strategies.

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Informed Consent: Signed consent was obtained from the patient's guardian.

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