Journal of Health Care Communications
ISSN: 2472-1654

Open access Review Article

Development of a Predictive Mortality Scale in Patients with Neutropenic Enterocolitis: A Systematic Review

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ABSTRACT

Introduction: Neutropenic Enterocolitis (NE) is a severe complication in immunosuppressed patients, especially those undergoing intensive oncological treatments. Predicting mortality in these patients is crucial for optimizing clinical management and improving therapeutic outcomes.

Methods: We conducted a systematic review of 24 clinical studies, including 1,172 patients diagnosed with neutropenic enterocolitis. Data sources included PubMed and Google Scholar, with the last search performed on September 13, 2024. Studies were selected based on inclusion criteria, such as adult patients, availability of mortality data, and the use of G-CSF, while exclusion criteria included pediatric populations and case reports. Clinical variables analyzed included ICU admission, surgical management, comorbidities, severity of neutropenia, and diagnostic timing.

Results: A total of 14.40% of patients required ICU admission, and 43% needed surgical management. Mortality was 23.60%, and the use of G-CSF significantly reduced mortality (10.75% vs 44.44%, $p<0.001$). Late diagnosis was associated with higher mortality (48.28% vs 15.56%, $p<0.01$). A predictive scale based on these risk factors stratified mortality risk into low, moderate, and high categories.

Conclusion: The proposed scale shows potential for identifying patients at high mortality risk, allowing for more personalized interventions. External validation is needed to confirm its effectiveness.

Keywords: Neutropenic enterocolitis; Mortality; Predictive scale; Intensive care; G-CSF; Comorbidities

INTRODUCTION

Neutropenic Enterocolitis (NE), often referred to as typhlitis, is an acute inflammatory condition of the intestine, predominantly affecting the cecum and surrounding structures. It is most commonly seen in patients with profound neutropenia, particularly those undergoing aggressive treatments for hematological malignancies such as acute myeloblastic leukemia (AML) [1,2]. The condition is associated with a high risk of morbidity and mortality, presenting a significant clinical challenge due to its nonspecific symptoms-fever, abdominal pain, diarrhea, and signs of sepsis [3,4].

Early recognition of risk factors that predict mortality in patients with NE is critical for optimizing therapeutic strategies and improving patient outcomes. Despite several studies identifying individual risk factors, there is no standardized tool for predicting mortality in these patients. This study aims to address this gap by conducting a systematic review of available clinical data to develop a predictive mortality scale for patients with neutropenic enterocolitis.

Received:	24-September-2024	**Manuscript No:**	IPJHCC-24-21607
Editor assigned:	26-September-2024	**PreQC No:**	IPJHCC-24-21607 (PQ)
Reviewed:	10-October-2024	**QC No:**	IPJHCC-24-21607
Revised:	15-October-2024	**Manuscript No:**	IPJHCC-24-21607 (R)
Published:	22-October-2024	**DOI:**	10.36846/2472-1654-9.5.41

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Citation Bórquez RZ, Ramirez AF, Jasso OS, Trujillo EP, Pérez YJS (2024) Development of a Predictive Mortality Scale in Patients with Neutropenic Enterocolitis: A Systematic Review. J Healthc Commun. 9:41.

LITERATURE REVIEW

Study Design

This study follows a systematic review methodology, complying with the PRISMA 2020 guidelines. We included data from 24 clinical studies, representing a total of 1,172 patients diagnosed with neutropenic enterocolitis. The primary objective was to identify risk factors associated with mortality and use these factors to develop a predictive scale (**Figure 1**).

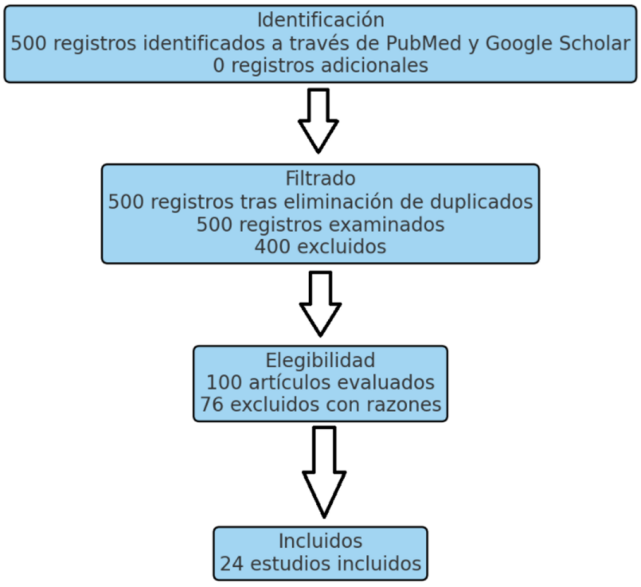

Figure 1: PRISMA flow diagram showing the study selection process for the systematic review

Eligibility Criteria

Studies were included if they met the following inclusion criteria:

- **Population:** Adult patients diagnosed with neutropenic enterocolitis.
- **Outcomes:** Mortality rates and related clinical outcomes.
- **Intervention:** Use of granulocyte colony-stimulating factor (G-CSF).
- **Study type:** Clinical studies with available mortality data.

Studies involving pediatric patients, and those lacking full-text access were excluded.

Information Sources

The systematic search was conducted using PubMed and Google Scholar, with the last search performed on September 13, 2024. No language restrictions were applied; However, only studies published from 2005 onwards were included in the analysis to ensure the relevance of data to current clinical practice.

Search strategy: The search strategy was developed using key terms such as "neutropenic enterocolitis," "typhlitis," and "neutropenic colitis." Boolean operators (AND, OR) were used to combine search terms. Filters were applied to include studies published from 2005 to 2024. Search strings included:

- ("neutropenic enterocolitis" OR "typhlitis" OR "neutropenic colitis") and ("mortality")
- The search strategy was applied across PubMed and Google Scholar, yielding a total of 500 studies.

Selection process: Two independent reviewers screened titles and abstracts of all identified studies. Full-text articles were assessed for eligibility, with disagreements resolved through discussion or consultation with a third reviewer. An Artificial Intelligence (AI)-based tool was employed to assist in screening and study selection, reducing bias and increasing efficiency. A PRISMA flow diagram is provided in **Figure 2**, illustrating the selection process from initial search to final inclusion.

Figure 2: 3D Surface Plot: Mortality vs Risk Score and Diagnosis Timing: This 3D plot visualizes how mortality rates change with risk score and diagnosis timing. As the risk score and diagnosis delay increase, mortality rises significantly, as shown by the surface's gradient

Data collection process: Data were extracted independently by two reviewers using a standardized data extraction form, ensuring that key variables, such as mortality rates, use of G-CSF, ICU admission, and surgical management, were captured. Any discrepancies were resolved by discussion.

Data items: The primary outcomes assessed were mortality rates, ICU admission, and the need for surgical management. Additional data items collected included patient demographics (age, gender), severity of neutropenia (absolute neutrophil count <500 cells/mm^3), and comorbidities (e.g., diabetes, renal disease).

Risk of bias assessment: The risk of bias in the included studies was assessed using the Newcastle-Ottawa Scale for observational studies. This tool evaluates the selection of study groups, comparability, and ascertainment of outcomes. Two reviewers independently assessed the studies for bias, with disagreements resolved by consensus.

Effect measures: The effect measures used in this systematic review included risk ratios (RR) and odds ratios (OR), with corresponding 95% confidence intervals (CI), to assess the relationship between clinical variables and mortality.

Evaluated variables: Demographic variables:

- Average age: 42.04 years
- Gender: 58.28% males and 41.72% females

Clinical variables:

- Need for intensive care (ICU/ITU): 14.40%
- Need for surgical management: 43% (9% excluding study C2; 17.9% in studies with intermediate data)
- Average mortality: 23.60%
- Cure rate: 76.26%
- Response rate to conservative treatment: 74.10%
- Comorbidities: 100% with hematological cancer, mainly acute myeloblastic leukemia (AML)
- Severe neutropenia (ANC <500 cells/mm³): 87.39%, with mortality in deep and severe neutropenia of 23.53% and 13.33% (P=0.08)
- Use of hematopoietic growth factors (G-CSF): 91.18%, with mortality of 10.75% in this group versus 44.44% in those who did not receive it (p<0.001)
- Early diagnosis (<24 hours): Mortality of 15.56% vs. late diagnosis (>24 hours): 48.28% (p<0.01)
- Diagnostic methods used: CT (61.39%), USG (44.06%), abdominal X-ray (57.43%)
- Persistent symptoms: 10.14%

RESULTS

Study Selection

Out of 500 records identified in the initial search, 100 full-text articles were assessed for eligibility, and 24 studies met the inclusion criteria. **Figure 3** illustrates the PRISMA flow diagram detailing the study selection process.

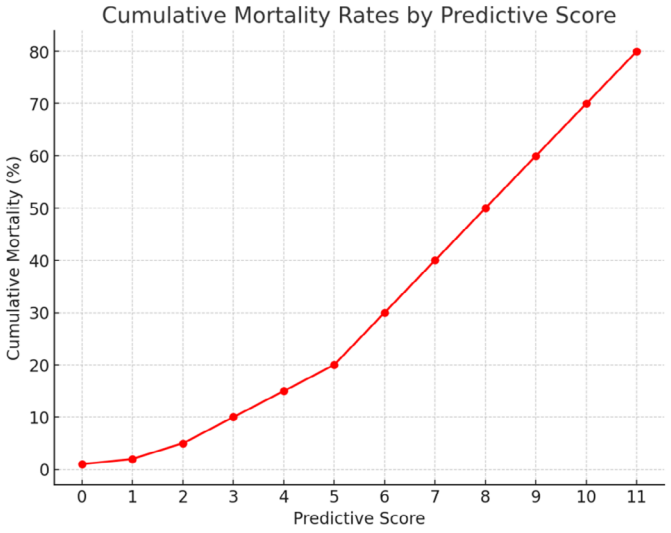

Figure 3: Cumulative Mortality Rates by Predictive Score: A line chart demonstrating how mortality rates increase cumulatively as the predictive score rises, highlighting the progressive risk of mortality

Study Characteristics

The included studies comprised a total of 1,172 patients, with a mean age of 42.04 years. Of these patients, 58.28% were male and 41.72% female. The majority of patients (87.39%) had severe neutropenia (absolute neutrophil count <500 cells/mm³), and all were undergoing treatment for hematological malignancies, primarily AML. **Table 1** summarizes the key characteristics of the included studies.

Risk of bias in studies: The results of the Newcastle-Ottawa Scale assessment revealed a low risk of bias in most studies regarding the selection of patient cohorts and ascertainment of outcomes. However, several studies presented a high risk of bias due to incomplete data reporting and lack of control for confounding variables.

Table 1: Point assignment

Risk Factor	Description	Points	Justification
Advanced age	Age ≥ 60 years	1	Clinically relevant association; mortality in adults: 16.43% vs. pediatric: 17.95% (not significant)
Deep neutropenia	ANC <100 cells/mm³	2	Mortality in deep neutropenia: 23.53% vs. severe: 13.33% (strong trend)
Presence of comorbidities	Diabetes, renal disease, etc.	2	Mortality in patients with comorbidities: 50% vs. without: 19.67% (significant)
Presence of concomitant infections	Bacteremia, fungemia, etc.	1	Mortality with infections: 60% vs. without: 13.73% (significant)
Use of intensive chemotherapy	Treatments with agents like Cytarabine	1	Mortality with Cytarabine: 31.25% vs. Anthracyclines: 20% (trend)
Need for intensive care (ICU/ITU)	Admission to ICU/ITU	2	Mortality in ICU patients: 30% vs. non-ICU: 16% (estimated)
Late diagnosis	NE diagnosis>24 hours post-chemotherapy	1	Late diagnosis associated with significantly higher mortality (48.28% vs. 15.56%, p<0.01)
Need for surgical management	Required surgery (e.g., colectomy,laparotomy)	1	Mortality in surgery: 55.60% vs. no surgery: 23.60% (significant)

Mortality outcomes: The overall mortality rate across the included studies was 23.60%. Patients requiring ICU admission had a significantly higher mortality rate compared to those who did not require ICU care (30% vs. 16%, p<0.001). The use of G-CSF was associated with a significant reduction in mortality (10.75% in G-CSF users vs. 44.44% in non-users, p<0.001). Late

diagnosis, defined as diagnosis more than 24 hours after the onset of symptoms, was also strongly associated with increased mortality (48.28% vs. 15.56%, p<0.01).

Development of predictive mortality scale: Based on the analysis of the identified risk factors, a predictive mortality scale was developed. Points were assigned to each risk factor according to the strength of association with mortality.

Statistical analysis: Chi-square tests and Fisher's exact test were used to evaluate associations between categorical variables and mortality. Statistical significance was established at p<0.05. Analyses were performed using Python software version 3.12.6.

Interpretation of total score:

- 0-2 Points: Low Risk (Mortality ≤10%)
- 3-5 Points: Moderate Risk (Mortality 11-30%)
- 6-8 Points: High Risk (Mortality>30%)
- 9-11 Points: Very High Risk (Mortality>50%)

DISCUSSION

This multicentric retrospective study identified and quantified risk factors associated with mortality in patients with neutropenic enterocolitis. The developed predictive scale demonstrates promising capability to stratify mortality risk, facilitating more informed and timely clinical decision-making [5] (**Appendix 1**).

Main Findings

1. **Use of G-CSF:** A significant association was observed between the use of hematopoietic growth factors and lower mortality, supporting their use in NE management [6].
2. **Early diagnosis:** Diagnosis within the first 24 hours post-chemotherapy was associated with a significant reduction in mortality, emphasizing the importance of rapid identification and treatment of NE [7].
3. **Need for intensive care:** ICU/ITU admission was a strong predictor of mortality, indicating that these patients present with more severe clinical conditions [8].
4. **Deep neutropenia and comorbidities:** Both factors showed a robust association with mortality, highlighting the need for careful evaluation and aggressive management in these patient subgroups [9,10].

Limitations

- **Aggregated data:** The retrospective nature and use of aggregated data limit the ability to perform detailed multivariate analyses.
- **Heterogeneity among studies:** Variations in inclusion criteria and diagnostic methods across studies may have introduced biases and variability in results [11].
- **Data overlap:** Potential overlaps in data from certain studies could have affected the accuracy of estimates [12].
- **Clinical implications:** Implementing this predictive scale in clinical settings could enhance risk stratification and guide more targeted interventions, such as the preventive use of G-CSF, intensive monitoring, and informed decisions regarding surgical management [6,13].

Recommendations for future research:

1. External validation: Validating this scale in an independent cohort is crucial to confirm its accuracy and reliability.
2. Prospective studies: Designing prospective studies with individual-level data collection will allow for more robust analyses and precise scale adjustments.
3. Incorporation of biomarkers: Evaluating the inclusion of inflammatory biomarkers could enhance the predictive accuracy of the scale.
4. Standardization of variables: Ensuring uniform definitions for key variables, such as severe neutropenia and early diagnosis, will reduce heterogeneity among studies.

CONCLUSION

The predictive mortality scale developed in this study offers a preliminary tool for identifying NE patients at high risk of mortality. Factors such as deep neutropenia, comorbidities, need for intensive care, use of G-CSF, and late diagnosis are essential for risk stratification. Although the scale shows potential, external validation and refinement through future studies with more detailed and consistent data are required.

FUNDING INFORMATION

No funding sources were involved in this study.

CONFLICT OF INTEREST

The authors declare no competing interests related to this study. There are no financial or personal relationships with other people or organizations that could inappropriately influence (bias) our work.

Ethical Approval

The study was conducted in accordance with ethical standards. This study is a retrospective analysis based on anonymized data that had been previously collected. Formal Institutional Review Board (IRB) approval was not required according to the ethical guidelines of the National Institute of Medical Sciences and Nutrition Salvador Zubirán, which provided an exemption from review for this type of study.

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