CLINICAL CHARACTERISTICS AND MORTALITY PREDICTORS OF ACUTE RESPIRATORY DISTRESS SYNDROME PATIENTS IN ICU- AN OBSERVATIONAL STUDY

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ABSTRACT

Introduction

Adult respiratory distress syndrome (ARDS) is an inflammatory lung condition characterized by a sudden onset of severe oxygen deficiency, bilateral chest infiltrates, and high morbidity and mortality rates. The causes and prognostic factors for ARDS may vary in tropical regions.

Objective

This study aimed to investigate the causes, clinical characteristics, and outcomes of ARDS patients admitted in ICU.

Methodology

We conducted a prospective observational study involving 92 ARDS patients admitted to the medical and surgical intensive care units of a tertiary care hospital in eastern Nepal from 2021 to 2023. We included patients aged 15 years and above who met all the Berlin criteria for ARDS. Patients with burns, end-stage renal disease, hepatic disease, head injuries, congestive cardiac failure, and postoperative patients were excluded. We assessed demographic parameters, initial clinical presentations, causative agents, ventilation parameters, organ failure during the ICU stay, and factors influencing patient mortality.

Result

Our cohort had a mean age of 45.71 ± 20.02 years, with a predominance of male patients. The majority of patients presented with fever and shortness of breath. Approximately 26.1% had mild ARDS, while 25% had severe ARDS. The initial Sequential Organ Failure Assessment (SOFA) score was 10.11 ± 6.07, with most patients having a lung injury score of less than 2.5. Higher lung injury scores and low PaO2/FiO2 ratios were associated with increased mortality (P<0.05). The overall mortality rate in our study was 33.6%.

Conclusion

Pneumonia emerged as the most common cause of ARDS in our region. Low PaO2/FiO2 ratios and higher lung injury scores significantly influenced ARDS mortality.

KEY WORDS

ARDS, acute lung injury, clinical characteristic, mechanical ventilation, outcome

INTRODUCTION

Acute Respiratory Distress syndrome (ARDS) is a frequently encountered clinical condition leading to acute respiratory failure among critically ill patients in the Intensive Care Unit.[1] ARDS is characterized by rapid onset of respiratory distress within one week which is associated with the gradual spread of abnormal infiltrations in both lungs. Notably, the low oxygen levels and the bilateral lung infiltrations are not caused by cardiogenic pulmonary edema.[2,3] Individuals suffering from ARDS exhibit a range of lung-related conditions that culminate in the emergence of severe, unresponsive oxygen dificiency diffuse damage to the alveoli, heightened permeability of pulmonary blood vessels and reduced lung flexibility. The initial documentation of ARDS dates back to 1967 when Ashbaugh and a group of colleagues identified 12 patients who displayed symptoms such as rapid breathing, persistent oxygen deficiency that did not improve with standard treatments and widespread haziness on chest X-rays following infections or traumatic events.[3] Quantifying the degree of lung injury, particularly in terms of vascular permeability and inflammatory responses, proves to be quite challenging. Therefore, the primary means of diagnosing ARDS relies on evaluating clinical symptoms and observing radiological alterations in the lungs. The most comprehensive clinical description of ARDS is outlined in the 2012 Berlin definition, which categorizes the spectrum of lung injury into mild, moderate, and severe based on the severity of hypoxia.[2] The degree of hypoxia is measured by ratio of partial pressure of arterial oxygen and fraction of inspired oxygen (Pa02 /FI02) and PaO2 / FlO2 less than 300 is characterized as acute lung injury.

Lung injury in ARDS can stem from a multitude of factors. Both infectious and non-infectious circumstances can trigger direct or indirect harm to the lungs, resulting in the clinical and pathological characteristics of ARDS. Pneumonia and aspiration are commonly recognized as primary culprits for direct lung injury, whereas sepsis syndrome stands out as the predominant contributor to indirect ARDS onset.[4] In rural tropical regions, tropical infections such as malaria, kala-azar, leptospirosis and dengue can play a significant role in the development of ARDS.[5] Recently, severe corona virus disease (COVID-19) can lead to ARDS like lung injury. However, delayed onset of bilateral pulmonary infiltrates and hypercoagulable profile have obscured the utility of traditional ARDS therapies in COVID-19 ARDS.[6]

ARDS can result in a pronounced inflammatory reaction, leading to the onset of multiorgan failure and a substantial mortality rate, which can range from 40% to 60%.[7,8] However, with improved comprehension of the underlying pathophysiology, advancements in mechanical ventilation techniques, and therapeutic interventions such as early proning, the mortality rate has notably decreased to a range of 9% to 20%. Several research studies have indicated that the initial oxygenation level or lung injury score lacks prognostic significance in predicting mortality. Nevertheless, the failure to achieve improved oxygenation or having a low lung injury score in the following days does indeed contribute to unfavorable patient outcomes.[9]

The objective of this study was to assess the clinical attributes, encompassing causes and clinical manifestations of ARDS patients as well as to analyze the factors that impact the mortality of ARDS patients treated in the ICU over a two-year period.

METHODOLOGY

This prospective observational study was conducted over a two-year period, spanning from 2021 March to March 2023, in the medical and surgical ICUs of a tertiary care hospital located in the eastern region of Nepal. Ethical approval was obtained from the institutional research committee (IRC - PA-005/2075-76). Informed and written consent was obtained from either the patient or their designated next of kin.

In our study, we employed the Berlin classification to diagnose and categorize ARDS patients. We included individuals aged 15 years and above who met all the criteria outlined in the Berlin classification for the diagnosis of ARDS. Patients with conditions such as burns, end-stage renal disease, hepatic disease, head injuries, congestive cardiac failure and those who had undergone surgery were excluded from our study. Patients were admitted to the ICU from various sources, including the emergency department, surgical wards and medical wards of the hospital. Upon admission to the ICU, a comprehensive assessment was conducted involving a detailed medical history, physical examination and systemic evaluation. Patients with ARDS were identified based on their medical history, chest X-ray results and arterial blood gas findings.

We collected baseline demographic information, noted any pre-existing medical conditions and performed initial investigations, which included complete blood counts, electrolyte levels, liver function tests and renal function tests. Additionally, we assessed the initial SOFA score upon admission. Bedside echocardiography was employed to rule out fluid overload and heart failure.

The choice of respiratory support, whether non-invasive or invasive ventilation was determined based on clinical indicators of respiratory failure and arterial blood gas analysis. Major therapeutic decisions were collaboratively made by intensivists and primary physicians. Within 48 to 72 hours of admission, all patients were reevaluated, and their findings were documented, including any signs of organ failure, ventilator parameters (if applicable), and lung injury scores.

Ultimately, we evaluated the clinical outcomes of the patients, considering mortality and any factors contributing to morbidity and mortality. Based on mortality outcomes, we categorized the included patients into survival and non-survival groups and we conducted comparisons to assess the impact of various independent variables on mortality prediction.

Patient data was collected and recorded in Microsoft Excel, after which it underwent statistical analysis utilizing IBM

SPSS version 21. To compare continuous variables, we employed either the student t-test or the Mann-Whitney U test, depending on the characteristics of the data. For comparing proportions, we used either the chi-square test or the Fisher exact test, selecting the most appropriate test for each specific analysis.

We conducted a 30-day survival analysis and assessed the lung injury score and the severity of ARDS between survivors and non-survivors using the Kaplan-Meier method and Cox regression analysis. A significance level of $p<0.05$ was considered as the threshold for statistical significance.

RESULTS

Over a period of two years, there were a total of 868 ICU admissions from the emergency department and different wards. Among these admissions, 124 patients were identified with ARDS based on the Berlin criteria. However, only 92 of these patients were ultimately included in the

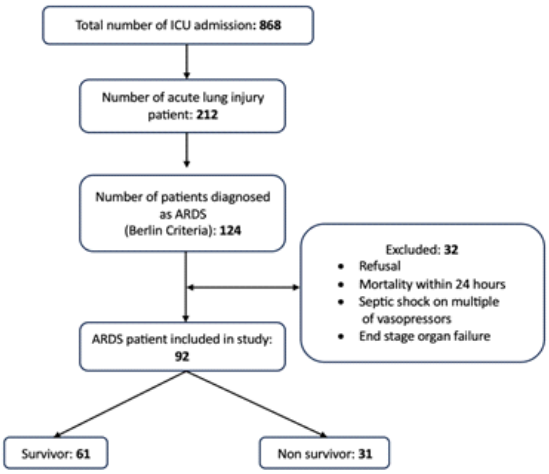

Figure 1: Flow diagram for study participants.

The average age of individuals in our cohort was approximately 45.71 years with 62% being male and 38% female. The most common initial symptoms reported by the majority of patients were fever (59.8%) followed by shortness of breath (47.8%) cough (41.3%), altered mental status (19.6%) and chest pain (16.3%). Among the comorbidities observed, hypertension (33.7%) was the most prevalent followed by diabetes (32.6%) and COPD (30.4%) within the study group.

We employed the Berlin criteria to stratify our patient cohort according to the severity of Acute Respiratory Distress Syndrome (ARDS) based on their initial arterial blood gas measurements. Specifically, 26.1% of the patients were diagnosed with mild ARDS, 42.4% with moderate ARDS, and 25% with severe ARDS. Among the 92 patients, we focused our severity analysis on the 86 individuals who had a PaO2/FiO2 ratio less than 300. The average initial SOFA (Sequential Organ Failure Assessment) score was 10.11 6.07, as shown in Table 1.

Tables 1: Demographic and clinical profiles

Variables		Values
Age (years)		45.71 ± 20.02
Sex	Male	57 (62%)
	Female	35(38%)
Clinical features		
Fever		55(59.8%)
SOB		44(47.8%)
Cough		38(41.3%)
Chest pain		15(16.3%)
Altered sensorium		18(19.6%)
SOFA		10.11±6.07
Comorbidities		
HTN		31(33.7%)
DM		30(32.6%)
IHD		16(17.4%)
CRF		10(10.8%)
Asthma		20(21.7%)
COPD		28 (30.4%)
Dyslipidemia		18(19.6%)
Lung injury	<2.5	48(52.2%)
	>2.5	44(47.8%)
Severity of ARDS	Mild	24(26.1%)
	Moderate	39(42.4%)
	severe	23(25%)

Note: SOB; shortness of breath, SOFA; sequential organ failure assessment, HTN; hypertension, DM; diabetes mellitus, IHD; ischemic heart disease, CRF; chronic renal failure, COPD; chronic obstructive pulmonary disease

As depicted in Table 2, a significantly high proportion of patients, specifically 93.3%, had an infectious origin for their ARDS. Among these cases, the most common infection leading to ARDS was community-acquired pneumonia (28.2%), followed by hospital-acquired pneumonia (17.3%), dengue fever (10.8%), leptospirosis (5.8%), malaria (3.4%), and a single patient who developed ARDS due to dengue infection. Within the infectious etiology category, sepsis syndrome, encompassing septicemia and septic shock, accounted for 19.5% of cases.

Among the non-infectious causes, poisoning was the primary culprit (11.9%), followed by trauma (10.8%), gastric aspiration (8.6%), pancreatitis (6.5%), and blood transfusion (2.1%).

Tables 2: Etiology of ARDS.

Infectious		Number of patients	Noninfectious	Number of patients
Pneumonia			Poisoning	11(11.9%)
	CAP	26 (28.2%)	Gastric Aspiration	8 (8.6%)
	HAP	16 (17.3%)		
Tropical infections			Trauma	10 (10.8%)
	TB	8 (8.6%)	Pancreatitis	6(6.5%)
	Leptospirosis	5 (5.4%)		
	Malaria	3 (3.2%)	Blood Transfusion	2 (2.1%)
	Dengue	10 (10.8%)		
Sepsis syndrome		18 (19.5%)		
Total		**86 (93.3%)**		**37(40.2%)**

Note: CAP; community acquired pneumonia, HAP; hospital acquired pneumonia, TB; tuberculosis

The patient cohort was divided into two groups: a survival group consisting of 61 individuals (66.3%) and a non-survival group comprising 31 individuals (33.6%), based on their mortality outcomes. We conducted a comparative analysis of various independent variables to assess their contribution to predicting mortality.

Significant differences in mortality were observed in cases with a higher lung injury score (greater than 2.5) and severe ARDS (PaO2/FIO2<100) (p<0.05). Interestingly, the use of prone ventilation did not yield a reduction in mortality (Table 3).

Table 3: Comparison of clinical parameters and comorbidities for mortality

Parameters			Survival	Non survival	P Value
Age					
Sex	male		42(45.7%)	15(16.3%)	0.100
	female		20(21.7%)	15(16.3%)	
HTN			18(19.5%)	21(22.8%)	0.062
DM			17(18.5%)	13(14.1%)	0.457
IHD			11(12.1%)	8(8.6%	0.731
CRF			12(13%)	7(7.6%)	0.784
COPD			18(19.6%)	10(10.9%)	0.809
Asthma			11(12%)	9(9.8%)	0.191
Dyslipidemia			12(13%)	6(6.5%)	0.842
Lung Injury score	<2.5		37(40.2%)	11(12%)	0.047
	>2.5		25(27.2%)	19(20.7%)	
Severity of ARDS		Mild	20(23.3%)	4(4.7%)	0.038
		Moderate	24(27.9%)	15(17.4%)	
		Severe	12(14%)	11(12.8%)	
Pa02/FIO2			186.09±77.98	136.23±60.10	0.003
Prone Ventilation			34(37%)	16(17.4%)	0.892

Note: HTN; hypertension, DM; diabetes mellitus, IHD; ischemic heart disease, CRF; chronic renal failure, COPD; chronic obstructive pulmonary disease.

We assessed the outcome variables, including 30-day mortality, the duration of ICU-stay, the length of mechanical ventilation, and the occurrence of various organ failures during the course of treatment. However, there were no significant differences in these parameters observed between the survivors and non-survivors, as indicated in Table 4. Though patient in survival group had longer survival days as compared to survival but the comparison was statistically non-significant.

Table 4: Comparison of outcome variables for mortality

Variables	Survival	Non survival	P Value
Length of MV stay	7.54±4.75	6.70±4.47	0.416
Length of ICU stay	10.37±6.89	7.96±5.26	0.095
AKI	19(30.6%)	11(12%)	0.564
Circulatory collapse with vasopressor therapy	26(28.3%)	9(9.8%)	0.269
Hepatic failure	19(20.7%)	5(5.4%)	0.152
CNS	11(12%)	7(7.6%)	0.526
Coagulopathy	12(13%)	8(8.7%)	0.425
Survival days	10.29±6.97	7.96±5.26	0.110

Note: MV; mechanical ventilation, AKI; acute kidney injury, CNS; central nervous system `

Survival analysis for lung injury score

The Kaplan-Meier test results, as shown in Table 5 and figure 2, revealed a significant difference in terms of 30-day survival when considering the lung injury score. Patients with a lung injury score less than 2.5 had a mean survival duration of 20.34 days, while those with a lung injury score exceeding 2.5 had a mean survival of 14.61 days (p=0.048).

Table 5: Log Rank (Kaplan Meier test) for Survival analysis for Lung Injury score

Group	Mean (days)	Std.error	CI 95%	P Value
Less than 2.5	20.34	1.81	16.788-23.903	0.048
More than 2.5	14.61	1.66	11.349-17.883	

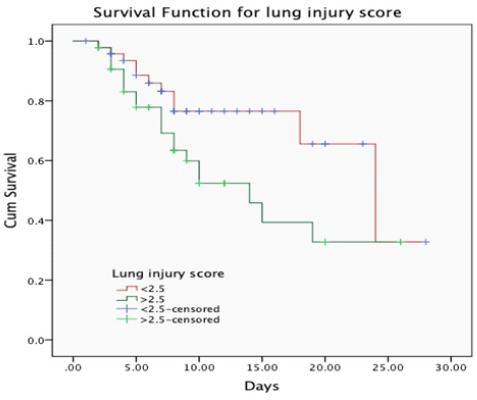

Figure 2: Kaplan Meier test for survival analysis for lung injury score

Survival analysis was conducted using the Kaplan-Meier test, specifically examining the survival duration based on the severity of ARDS, and the log-rank test was applied (as presented in Table 6 and Figure 3). The findings revealed a significant difference, with severe ARDS patients exhibiting a notably shorter mean survival duration of 11.40 days. In contrast, moderate ARDS patients had a mean survival duration of 19.75 days, and mild ARDS patients had a mean survival duration of 20.16 days, with a p-value of 0.003.

Table 6: Log Rank (Kaplan Meier test) for Survival analysis for severity of ARDS

Group (ARDS)	Mean (days)	Std.error	CI 95%	P Value
Mild	20.16	2.67	14.82-20.18	0.003
Moderate	19.75	1.71	16.40-23.11	
Severe	11.40	1.79	7.88-14.93	

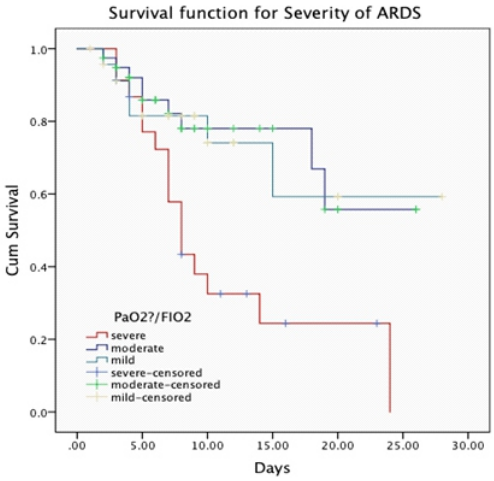

Figure 3: Kaplan Meier test for survival analysis for severity of ARDS

DISCUSSION

Our study aimed to investigate the etiology, clinical manifestations, and prognosis of individuals in a tropical locale. Analyzing data over a two-year period, we identified that 14.2% of all admissions to the intensive care unit (ICU) were associated with acute respiratory distress syndrome (ARDS), underscoring the significant prevalence of this condition within our region. It is worth noting that our patient cohort exhibited a notable predominance of male individuals, a trend consistent with the outcomes of studies conducted on a global scale.[2,8-10]

The higher proportion of male patients in our study may be attributed to various factors, such as differences in behavior and healthcare-seeking patterns. Men are generally more prone to engage in risky behaviors, including smoking and alcohol consumption, which can increase the risk of respiratory diseases. Furthermore, gender disparities in healthcare utilization may result in delayed medical intervention for women. These findings underscore the need for tailored public health initiatives and further investigation into gender-specific factors influencing the incidence and outcomes of ARDS in our region.

Our patient population had an average age of 45.71 years, and there was a predominance of males, a trend that aligns with the results reported in the ARDS Network trial (with an average age of 51 years) and the KCLIP studies (with an average age of 61 years).[11,12] One potential explanation for this pattern may be that young males in our region are more actively engaged in outdoor environments, potentially increasing their exposure to environmental hazards and vectors of infectious diseases. Among our patients, the most frequent initial symptoms reported were shortness of breath and fever, and the majority of them fell into the mild ARDS category based on the PO2/FIO2 ratio.

In our study, the leading cause of lung injury was of infectious origin, with the majority of infection-related cases being attributed to community-acquired pneumonia, followed by hospital-acquired pneumonia. The prevalence of tropical infections such as tuberculosis, dengue, leptospirosis, and malaria were notably high due to the low socioeconomic status and geographical factors, making them significant contributors to the etiology of ARDS. Dengue, in particular, had a relatively high incidence in our setting, leading to a significantly larger number of patients developing ARDS as a result.[13] In terms of infectious causes, sepsis syndrome played a significant role in contributing to ARDS. A study conducted in Iceland indicated that ARDS was more prevalent in cases of pneumonia and sepsis, while another research study conducted in Australia revealed that sepsis (32%) was the primary underlying cause of ARDS, closely followed by pneumonia (30%).[14,15] In our study, we observed that 28% of ARDS cases were attributed to tropical infections, a finding consistent with a study in South India, where tropical infections accounted for 26% of all ARDS cases.[16] Notably, a previous study identified malaria as the leading cause of ARDS (27.6%), followed by leptospirosis (20.7%), and dengue (5.2%).[17] This highlights the substantial role of tropical infections in the onset of ARDS, especially in regions with a higher prevalence of such diseases. These findings underscore the importance of recognizing and addressing tropical infections as significant contributors to the burden of acute respiratory distress syndrome.

This can be linked to the heightened prevalence of these tropical diseases in Asia, which is due to the favorable climatic conditions that support both the disease-causing agents and their vectors.

Likewise, non-infectious causes accounted for 40.2% of the etiology in our study, with acute poisoning being the primary contributor. In our region, there was a notably high incidence of organophosphorus poisoning, which can directly lead to alveolar damage, increased capillary permeability and subsequently ARDS. Additionally, organophosphorus poisoning can also result in ARDS as a secondary consequence of aspiration.[18,19]

The recorded mortality rate in our study was relatively lower when compared to international data. In various other studies, the estimated mortality rate for ARDS typically ranges from 37% to 57%.[2,20,21] The lower mortality rate observed in our study may be attributed to differences in the baseline characteristics of the subjects, such as their relatively younger age, in comparison to the subjects in other studies. Furthermore, the diverse etiologies of ARDS in our study, including tropical diseases, could have influenced the outcomes.

The study findings indicated that a lung injury score exceeding 2.5 and the presence of severe ARDS (PaO2/FIO2< 100) had a noteworthy impact on the mortality of ARDS patients. Patients with higher lung injury scores and

lower PaO2/FIO2 ratios experienced elevated mortality rates ($p<0.05$). Additionally, individuals with higher lung injury scores and severe ARDS had significantly shorter survival durations. In a comprehensive analysis involving a large, multi-ICU patient cohort with ARDS, both the Lung Injury Score (LIS) and the severity stages defined by the Berlin criteria were associated with increased in-hospital morbidity and mortality.[22]

In a study conducted by Bhadade, it was observed that out of 51 patients with a PaO2/FiO2 ratio of 200 or less, 32 patients expired (67.2%), while only 1 out of 8 patients (12.5%) with a PaO2/FiO2 ratio greater than 200 succumbed to their condition. Interestingly, in the same study by Bhadade, the Lung Injury Score (LIS) was not identified as a valuable predictor of mortality.[20]

We noticed that a substantial portion of our patients experienced the development of one or more organ failures during their stay in the ICU. Many of our patients had hypotension, both systolic and diastolic dysfunction, necessitating the use of inotropic support, and this was often concomitant with acute kidney injury. However, we did not observe a significant difference in terms of mortality. In contrast, a study by Kraman et al. reported much higher mortality rates of 85.7% for hypotension and 80% for acute kidney injury (defined as creatinine levels exceeding 2 mg/dl).[23] In a separate study conducted by Brogan et al., it was revealed that the mortality rates in patients with ARDS who also had non-respiratory multi-organ failure increased with the number of organ failures. Specifically, the mortality rates were 56% for one organ failure, 72% for two organ failures, 84% for three organ failures, and 100% for four organ failures.[24]

CONCLUSION

In our study, the primary cause of ARDS was found to be community-acquired pneumonia followed by sepsis syndrome and tropical infections. The most frequent clinical presentation included fever and shortness of breath. This pattern in etiology reflects the geographical prevalence of these diseases and the presence of tropical vectors in our region. Furthermore, our study highlighted that the severity of ARDS (as indicated by the PaO2/FiO2 ratio), the lung injury score, and infectious etiologies were associated with poorer outcomes and could serve as individual predictors of mortality.

LIMITATION OF THE STUDY

Our study had several limitations. It was an observational study with a relatively small sample size, which lacked the statistical robustness required to draw definitive conclusions. We also could not explore various individual parameters, such as high or low TLC, acidosis, elevated lactate levels, SOFA score, or APACHE score, as potential indicators of mortality within our patient group. Moreover, due to the unavailability of an institutional laboratory facility, we were unable to investigate atypical organisms like Mycoplasma or Legionella or conduct the necessary tests to rule out viral or fungal causes of ARDS. These assessments could have yielded valuable insights into potential, yet undiagnosed, underlying causes of the condition

RECOMMENDATION

The groundbreaking discovery that pneumonia is the leading cause of Acute Respiratory Distress Syndrome (ARDS) in Nepal is of paramount significance. This emphasizes the urgent need to raise awareness among critical care physicians. With this knowledge, medical professionals are better equipped to make informed decisions and promptly initiate antimicrobial therapy for patients at risk of ARDS. This finding marks a pivotal moment in Nepal's medical landscape, underscoring the importance of pneumonia recognition, accurate diagnosis, and swift treatment. Increasing awareness among critical care physicians enhances the country's ability to combat ARDS effectively, leading to better patient outcomes and advancing critical care practices, ultimately ensuring the well-being of the population.

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CONFLICT OF INTEREST

None

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