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RESEARCH ARTICLE

The Pattern of Pediatric Acute Respiratory Distress Syndrome over 10 Years Period and Related Risk Factors of its Outcome Mortality

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Abstract:

Background:

Although paediatric acute respiratory distress syndrome (PARDS) is a common and devastating clinical syndrome that contributes to high morbidity and mortality, there is little known about its pattern and outcome mortality over time.

Objective:

This study aimed to determine the pattern of PARDS over a 10-year period and the risk factors for its outcome, mortality.

Methods:

This study was done at King Fahd University Hospital in Saudi Arabia using a retrospective study design involving children aged from > 2 weeks to 14 years admitted to the PICU due to PARDS. Over the last ten years, data was extracted from their medical records.

Results:

The number of PICU admissions over the last ten years was 2317, the rate of PARDS amongst PICU admissions was 376/2317 (16.23%), and mortality amongst PARDS cases was 83/376 (22.07%). ER admission route, chronic liver disease, sepsis, fluid overload, the number of inotropes 3, and pneumonia mediastinum were significant predictors of mortality in PARDS (p 0.001). In addition, the mean PRISM III score, PICU admission days, and ventilation days were higher in the deceased than in the survivors of PARDS. In contrast, the mean PaO₂/FIO₂ and oxygen saturation indices were significantly lower among the deceased than the survivors (p 0.01).

Conclusion:

Although the rate of PARDS was alarming, the number of PARDS deaths was constant over the study period. Sepsis, ER admission route, comorbidities, fluid overload, a higher PRISM III score, longer PICU admission, and ventilation days increased the risk of PARDS mortality.

Keywords: Children, PALICC definition, Death rate, Incidence, Prevalence, PICU.

Article History

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1. INTRODUCTION

Paediatric acute respiratory distress syndrome (PARDS) is a common and devastating acute clinical condition affecting medical and surgical patients and results in PICU admission and mechanical ventilation [1, 2]. Ashbaugh *et al.* (1967) were the first to describe acute respiratory distress syndrome (ARDS) as a syndrome that is characterized by tachypnea, hypoxia, and decreased pulmonary compliance [3]. PARDS

was recently defined as an acute onset of hypoxic respiratory failure with new infiltrate(s) on chest x-ray that is not fully explained by cardiac failure or fluid overload by the Pediatric Acute Lung Injury Consensus Conference (PALICC) [4]. Notably, this includes using the oxygenation index (OI) instead of the PaO₂/FiO₂ ratio, SpO₂-based indices, and less restrictive radiographic criteria [5]. It includes chronic lung disease (CLD) and cardiac conditions, which contribute to a significant number of patients with PARDS and were previously excluded in the Berlin and AECC definitions [6]. PARDS can be triggered by a heterogeneous set of causes, which can be classified as direct or indirect lung injury causes, both of which might end up with the influx of protein-rich

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edema fluid into the air spaces and increased vascular permeability, which may end up with hypoxic respiratory failure, sepsis, and pneumonia, which represent almost half of the primary causes [7, 8]. Despite decreasing mortality in PARDS over the past two decades [9, 10], it still appeared highly variable across studies. A meta-analysis by Wong et al. (2015) found the mortality rate in PARDS to be 24%, with an overall downtrend in mortality, especially for those children without pre-existing comorbidities [11]. It has been estimated that the frequency of pediatric ALI/ARDS in the United States, Europe, Australia, and New Zealand is 2.0–12.8 cases/105 person-years, with 18–27% overall ALI/ARDS estimated mortality [12, 13]. Recently, one of the largest international prospective studies of PARDS that used the newly adopted PALICC definition found that PARDS mortality exceeded 30% in pediatric patients with severe hypoxemia [13]. In addition, the following factors have been identified as significant predisposing risk factors for PARDS mortality: an immune-compromised state, multi-organ dysfunction, the severity of hypoxemia, and a high oxygen index at 24 h [11 - 14]. However, there has been little research into the pattern of PARDS and its outcome, mortality, in Saudi Arabia and elsewhere in recent years. This study aimed to determine the trend of PARDS and its outcome mortality using the last decade's data from a tertiary hospital in Saudi Arabia. In addition, it seeks to estimate the risk of mortality concerning several health indicators and socio-demographic features.

2. MATERIALS AND METHODS

2.1. Design

This study was done using a retrospective cohort study design by extracting data from the medical records of pediatric patients admitted to pediatric intensive care units (PICU) during the last ten years, from 2010 to 2019. This study was conducted at King Fahd University Hospital (KFUH) of Imam Abdulrahman bin Faisal University (IAU) after the approval of the IAU ethical review board (IRB 2020-01-213).

2.2. Data Collection

Medical records showed that children aged two weeks to fourteen years were admitted to the PICU due to: low oxygen saturation requiring oxygen support with an oxygenation index (OI) (FiO₂ mean airway pressure 100)/PaO₂; more than four or an oxygenation saturation index (OSI) (FiO₂ mean airway pressure 100)/SpO₂. More than 5 with a new lung infiltrate, (unilateral or bilateral) consistent with acute parenchymal disease occurring within seven days of a known insult and the edema not fully explained by fluid overload or cardiac failure was included. The definition used in this study of pediatric acute respiratory distress syndrome (PARDS) is proposed by the Pediatric Acute Lung Injury Consensus Conference Group (PALICC) [4]. The pediatric acute respiratory distress syndrome mortality was considered as the death occurred during PICU admission for children who were diagnosed with PARDS upon admission to PICU, and mortality risk was estimated in relation to the following possible risk factors; age, gender, etiology (sepsis, community-acquired pneumonia, trauma, drowning injuries, burns, inhalational injuries or

others), route of PICU admission (pediatric ward or pediatric ER), presence of comorbidities (no, congestive heart disease (CHD), chronic lung disease (CLD), or others) as well as with following possible PARDS related morbidities; sepsis (yes or no), fluid overload (yes or no), number of used inotropes, chest complications (normal, pneumomediastinum, subcutaneous emphysema, or pneumothorax) and PRISM III score. Finally, the PARDS mortality risk was estimated in relation to the number of days spent in the hospital (total days of hospital admission, PICU days number, and ventilation days number).

2.3. Data Analysis

The analyses were done using STATA software version 16 (StataCorp, 2019). The categorical variables, including mortality and risk factors, were presented as frequency and percentage. A chi-square or Fisher exact test was used to compare the distribution of risk factors and PARDS expected morbidities among the deceased and survivors. Numeric response variables like age, length of stay, and oxygen saturation were presented as mean and standard deviation. An unpaired t-test was applied to compare these variables between PARDS for the deceased and those who survived. In addition, unadjusted and adjusted regression models were established to estimate mortality risk among PARDS-diagnosed patients. The regression models were adjusted for age, gender, and weight upon admission. A statistically significant result was considered if the p-value was 0.05.

3. RESULTS

The total number of PICU admissions over the last ten years was 2317, with an average annual admission number of 232 (SD = 72, max = 355; min = 143). Out of these 2317 PICU-admitted children, there were n= 376 (16.23%) children with PARDS with an annual average number of admission equal to 38 (SD=7, max.=50, min.=30), Table 1. Additionally, the total number of deaths among PARDS patients over the last ten years was 83, or 22.07% of total PARDS admitted patients who died. On the other side, PARDS was the major reason for death among PICU admission, as 62.9% of total PICU deaths were due to PARDS. Although the number of PICU admissions increased over the last few years, the number of PICU deaths (mean=24, SD=35, min.=9, max.=123) and the number of PARDS deaths (mean=15.09, SD=22.62, max.=5, max.=83) remained almost the same. In this regard, the risk of death due to PARDS amongst the PICU-admitted patients during their PICU admission was ten times higher compared to PICU children who did not have PARDS (OR = 10.94, 95% CI = 7.53 to 15.90, p 0.001). Table 2 summarizes the socio-demographic features and health indicators of PARDS participants in relation to their mortality outcome. The mean age of PARDS participants was 3.84 years (SD = 3.83, min. = 0.2, max. = 14), and the mean weight was 19.25 kg (SD = 11.86, min. = 4, max. = 43), with no statistically significant difference between survived and deceased patients in regard to their weight and age. The mean hospital admission days were (mean=17.20, SD=5.021, max=32, min=6), and the mean PICU admission days were (mean=12.89, SD=4.20, max=31, min=6). The mean ventilation days were (mean=10.55, SD=3.86, max=25, min=5), with a statistically significant difference in

the mean ventilation days between males (mean=10.89, SD=4.09, max=25, min.=5) and females (mean=9.79, SD=3.38, max=21, min=6, x2 (374), p=0.028) The most common etiology of PADRS was infection (n = 199, 52.93%) followed by trauma (n = 59, 15.69%). The PARDS' most common route for PICU admission was through the pediatric ward (n = 220, 58.51%), while the most common associated comorbidity was CHD (n = 75, 43.10%). As seen in Table 3, PARDS mortality was statistically significantly common amongst children with sepsis (n = 45, 54.22%), children with fluid overload (n = 49, 59.04%), and children for whom they received three inotropes or above (n = 36, 43.37%). Furthermore, the deceased PARDS children had statistically significantly longer PICU admission days (mean = 16.48, SD = 0.70) and longer ventilation days (mean = 14.90, SD = 0.61) than the survivors. Additionally, their PRISM III score upon admission (mean = 17.71, SD = 0.60) was statistically

significantly higher than PARDS-surviving children. Regards to the risk of mortality amongst PARDS patients, as summarized in Table 4, the odds of mortality were higher in relation to the following medical events; ER admission route (Adjusted OR=4.00, 95% CI=2.37 to 6.78), presence of CHD (Adjusted OR=2.94, 95% CI=1.55 to 5.54) or CLD comorbidities (Adjusted OR=5.66, 95% CI=2.76 to 11.63), having fluid overload (Adjusted OR=3.21, 95% CI=1.94 to 5.32), presence of chest complication (Adjusted OR=6.260, 95% CI=2.60 to 15.03) presence of sepsis (Adjusted OR=3.50, 95% CI=2.11 to 5.83), receiving an inotrope (Adjusted OR=4.58, 95% CI=3.09 to 6.78), higher PRISM III score (Adjusted OR=1.24, 95% CI=1.17 to 1.30), longer days of PICU admission (Adjusted OR= 1.33, 95% CI=1.23 to 1.44) and longer ventilation days (Adjusted OR=1.59, 95% CI=1.42 to 1.78).

Table 1. Trend of Pediatric Acute Respiratory Distress Syndrome (PARDS) and its related mortality over the period of 2010-2019.

Calendar Year	Number of PICU Admissions	Rate of PARDS (%)	PICU Mortality rate (%)	PARDS Mortality rate (%)	PARDS mortality / PICU mortality (%)
2010	173	31 (17.9)	9 (5.2)	5 (16.1)	55.6
2011	168	44 (26.2)	18 (10.7)	10 (22.7)	55.6
2012	200	35 (17.5)	11 (5.5)	7 (20.0)	63.6
2013	143	31 (21.7)	14 (9.8)	8 (25.8)	57.1
2014	208	50 (24.0)	17 (8.2)	12 (24.0)	70.6
2015	257	30 (11.7)	15 (5.8)	9 (30.0)	60.0
2016	220	33 (15.0)	11 (5.0)	7 (21.2)	63.6
2017	245	40 (16.3)	17 (6.9)	11 (27.5)	64.7
2018	348	41 (11.8)	9 (2.6)	6 (14.6)	66.7
2019	355	41 (11.6)	11 (3.1)	8 (19.5)	72.7
Total	2317	376	132 (5.7)	83 (22.1)	62.9

Note: Values given in parentheses are percentages

Table 2. The sociodemographic features of study participants in relation to survival status (n=376).

Variables	Total (n = 376)	Survived (n= 293)	Deceased (n= 83)	P-value
Age				
o Infancy (≤1 year)	148	122 (82.4)	26 (17.6)	0.480
o Toddlerhood (>1-2 year)	55	42 (76.4)	13 (23.6)	
o Early childhood (>2-5 years)	62	48 (77.4)	14 (22.6)	
o Middle childhood (6-11 years)	91	66 (72.5)	25 (27.5)	
o Early adolescence (12-18 years)	20	15 (75.0)	5 (25.0)	
Gender				
o Male	236	182 (77.1)	54 (22.9)	0.624
o Female	140	111 (79.3)	29 (20.7)	
Etiology				
o Sepsis	111	61 (54.9)	50 (45.1)	0.938
o Community-Acquired Pneumonia	88	54 (61.4)	34 (38.6)	
o Trauma	59	35 (59.3)	24 (40.7)	
o Drowning or Submersion Injuries	23	12 (52.2)	11 (47.8)	
o Burns	14	8 (57.2)	6 (42.9)	
o Inhalational Injury	31	20 (64.5)	11 (35.5)	
o Others	50	30 (60.0)	20 (40.0)	

(Table 2) contd.....

Rout of Admission				
o Pediatric ward	220	192 (87.3)	28 (12.7)	<0.001
o Pediatric ER	156	101 (64.7)	55 (35.3)	
Comorbidity				
o No comorbidities	202	174 (86.1)	28 (13.9)	<0.001
o CHD	75	51 (68.0)	24 (32.0)	
o CLD	44	23 (52.3)	21 (47.7)	
o Others	55	45 (81.8)	10 (18.2)	

Table 3. Clinical factors related to mortality in PARDS (n=376).

Variables	Total (n = 376)	Survived (n= 293)	Deceased (n= 83)	P-value
Sepsis				
o Yes	119	74 (62.2)	45 (37.8)	<0.001
o No	257	219 (85.2)	38 (14.8)	
Fluid overload				
o Yes	140	91 (65.0)	49 (35.0)	<0.001
o No	236	202 (85.6)	34 (14.4)	
Number of inotropes				
o 0	16	12 (75.0)	4 (25.0)	<0.001
o 1	191	173 (90.6)	18 (9.4)	
o 2	128	103 (80.5)	25 (19.5)	
o 3 or above	40	4 (10.0)	36 (90.0)	
Complications				
o Normal	339	282 (83.2)	57 (16.8)	<0.001
o Pneumomediastinum	8	1 (12.5)	7 (87.5)	
o Subcutaneous emphysema	6	0 (0)	6 (100)	
o Pneumothorax	23	10 (43.5)	13 (56.5)	

Note: *Shows statistically significant result at 5% level of significance. Values given in parentheses are percentages.

Table 4. Risk estimation of ARDS related mortality in relation to identified risk factors and morbidities (n=376).

Predictors	Crude OR (95% C.I)	Adj. OR (95% C.I)
Age*	1.05 (0.99- 1.11)	1.04 (0.99- 1.11)
Gender (Female)**	0.88 (0.53-1.47)	0.88 (0.53-1.47)
Weight (kg)***	1.01 (0.99-1.03)	1.00 (0.96-1.04)
Etiology**** (Ref. Other etiology)		
o Sepsis	3.10 (1.21-7.98)	3.03 (1.17-7.86)
o Community-Acquired Pneumonia	2.44 (0.92-6.51)	2.36 (0.88-6.30)
o Trauma	1.68 (0.57-4.93)	1.66 (0.56-4.87)
o Drowning or Submersion Injuries	1.10 (0.25-4.85)	1.07 (0.24-4.76)
o Burns	1.22 (0.22-6.85)	1.19 (0.21-6.70)
o Inhalational Injury	1.76 (0.51-6.04)	1.75 (0.51-6.02)
Pediatric ward Rout of Admission****	3.73 (2.23-6.25)	4.00 (2.37-6.78)
Comorbidity**** (Ref. No comorbidity)		
o CHD	2.92 (1.56-5.48)	2.94 (1.55-5.54)
o CLD	5.67 (2.78-11.6)	5.66 (2.76-11.6)
o Others	1.38 (0.62-3.05)	1.39 (0.63-3.07)
Sepsis****	3.50 (2.11-5.81)	3.50 (2.11-5.83)
Fluid overload****	3.20 (1.94-5.29)	3.21 (1.94-5.32)
Complications (yes)****	6.43 (8.25-15.4)	6.25 (2.6-15.03)
Inotropes number****	4.55 (3.08-6.73)	4.58 (3.09-6.78)
PRISM III (score)****	1.23 (1.17-1.20)	1.24 (1.17-1.30)
Hospital admission days****	0.99 (0.94-1.04)	0.99 (0.95-1.04)

(Table 4) contd.....

PICU admission days****	1.30 (1.21-1.40)	1.33 (1.23-1.44)
Ventilation days****	1.54 (1.39-1.70)	1.59 (1.42-1.78)

Note: * Adjusted for gender, ** Adjusted for age, *** adjusted for age and gender, **** adjusted for age, gender, and weight.

4. DISCUSSION

Our study adds to the limited knowledge about the known epidemiology of PARDS, especially within the Middle East region, by describing the fluctuation in the number of PARDS cases and its outcome mortality over the last ten years using the PALICC definition among PICU children in Saudi Arabia. In our study, we reported the prevalence of PARDS over the study period to be 16.23%, while the yearly rate fluctuated between 11% and 26%. In the literature, the incidence of PARDS was estimated to vary between 2 and 12.8 per 100,000 people per year, or in other words, approximately 1 to 4% of PICU patients or 8 to 10% of mechanically ventilated patients, in studies that were done in the United States, Europe, Australia, and New Zealand using the AECC or Berlin definitions [15 - 17]. The high rate of our reported numbers could be attributed to using the newly adopted PALICC definition to define PARDS, which identifies significantly more patients than the AECC and Berlin definitions following the updated inclusion criteria [11, 18]. In addition, the newly adopted PALICC criteria had no upper limit on the included age group compared to the other two definitions [11, 18]. Two meta-analyses using the Berlin and AECC definitions revealed an apparent reduction in the overall mortality rate in children with PARDS over the past years, with the mortality rate cumulative estimate ranging between 20 and 30% [11, 18]. On the other side, studies that used the PALICC definition in the last several years identified almost similar numbers to our reported mortality; however, in the literature, there was significant regional heterogeneity in reported mortality. This variation was thought to be related to possible differences in the various healthcare systems' capabilities and the income disparities between regions or other unidentified factors [19]. Regardless of the reported reduction in PARDS mortality, the PARDS outcome mortality was still significant; hence, enhancements in early identification and assessment of morbidity and mortality risk factors and improving management will be mandatory to decrease the PRDAS mortality and morbidity burden [20 - 23]. Unfortunately, despite advances in diagnosing and managing PARDS, both mortality and morbidity rates remained high among patients [24, 25]. Our study found that the total number of PARDS deaths out of the total PICU mortality over the last ten years was 66%, while the total number of PARDS deaths out of all PARDS admitted cases was 22% over the last ten years. Nearly similar to our findings, Wong et al. (2016) reported in their study that the pooled PARDS mortality rate was around 24%, with a general mortality reduction over the last 30 years [11]. Nevertheless, it is still unclear if the main cause of mortality is due to PARDS itself, worsened by PARDS, or other comorbidities [26, 27]. Dowell et al. found in their large retrospective study that greater PARDS severity and higher PRISM scores were associated with earlier deaths as they reported an overall mortality rate of 19% and a median time to death of 6 days after PARDS onset [28]. In our study, we found that the risk of mortality amongst children with PARDS was

higher among those who presented through the ER, developed sepsis, had a high PRISM score for CHD or CLD, developed complications, had fluid overload, or received inotropes, and had longer PICU and/or ventilation days. The literature found that children with indirect lung injury (e.g., sepsis) had a threefold higher mortality risk than children with direct lung injury (e.g., pneumonia) when using the AECC and/or Berlin criteria to define PARDS [29]. In addition, these findings were also seen when PALICC definitions were used by several studies, as they suggested that higher initial severity of illness, more organ failure, and longer ventilation days were linked with a higher rate of mortality in children having extra-pulmonary PARDS [30]. Furthermore, lung infection (viral, bacterial, and/or fungal) was found to be the most common etiology of PARDS, accounting for two-thirds of reported PARDS cases among participants in the Pediatric Acute Respiratory Distress Syndrome Incidence and Epidemiology Study (PARDIE), followed by sepsis, which may cause diffuse alveolar damage in the alveolar epithelium membrane, resulting in hypoxia [4, 8]. Furthermore, mortality due to PARDS was significantly associated with organ failure, airway pressure gradient peak inspiratory pressure, and mechanical ventilation mean airway pressure gradient in the literature [8, 26]. On the other hand, many studies did not identify chronic diseases as contributing factors for the development of PARDS aside from chronic diseases that cause an immunodeficiency status. Regarding fluid overload as a risk factor for PARDS mortality, adult studies have found that an elevated accumulative fluid balance, particularly early-onset fluid overload, is associated with poor outcomes in patients with PARDS [30]. Recently, a systematic review study highlighted that the general effect of fluid overload on PARDS outcomes in pediatrics is relatively similar to the outcomes seen in adults [29]. Identifying and understanding the role of volume overload and other reported risk factors is important in developing an early interceptive measure and a preventive approach. On the other hand, we did not find a statistically significant difference in weight and age between surviving and deceased patients, even though current epidemiologic studies consistently identify age as an important factor in the development of PARDS, excluding those with a history of prematurity [8, 14, 29, 30]. However, our study found that the mean ventilation days and the mean PICU admission days were longer in deceased patients, and the mean ventilation days were slightly longer in male children. However, unlike our findings, recent pediatric data on ventilator-associated pneumonia from a prospective study in PICU children showed some evidence of worse outcomes (such as longer ventilation days, PICU admission days, and a higher mortality rate) in female patients [30 - 33]. These differences might be attributed to other variables that differ between the two genders and possibly affect the outcomes of PARDS, such as the etiology of PARDS and the presence of comorbid diseases. Although our study was the first national study in KSA and the Middle East that measured the pattern of PARDS over the last ten years, it was not without limitations. First, using a retrospective design

might precipitate measurement errors and affect the temporality of events and the data quality. A future prospective longitudinal design that reports the treatment modalities within the PICU setting would be recommended to enhance our understanding of treatment options for preventing mortality. In addition, involving one center might affect the external validity of our results; however, our center is considered one of the most advanced governmental tertiary hospitals in the Eastern Province and received referrals from all of the Eastern Province and, on some occasions, from other parts of the kingdom as well. A multicenter study would improve our knowledge regarding mortality prevention due to different applied treatment protocols within various PICU settings with different capabilities and experiences.

CONCLUSION

In conclusion, our study showed that the prevalence of PARDS over the last ten years was around 16% of our PICU admissions, and the yearly rate was dropping, especially over the last five years. However, the PICU mortality rate remained almost unchanged over the study period. The risk of mortality due to PARDS was higher with sepsis, pediatric ER admission routes, CHD and CLD comorbidities, fluid overload, a higher PRISM III score, longer PICU admission and ventilation days, and the presence of developed complications. Nevertheless, further research might be needed to understand the differences between our reported PARDS time pattern and the international pattern and the factors that might enhance different patterns of incidence and outcome mortality. Nursing may address this clinical condition by clearing the airway and ensuring appropriate breathing and circulation. When a child is in acute respiratory distress, a continuous pulse meter should be used to assess when therapy and support are needed.

LIMITATIONS OF THE STUDY

In this study, we could not cover all factors that might enhance different patterns of PARDS incidence and outcome mortality.

LIST OF ABBREVIATIONS

PARDS	= Paediatric Acute Respiratory Distress Syndrome
ARDS	= Acute Respiratory Distress Syndrome
PALICC	= Pediatric Acute Lung Injury Consensus Conference
CLD	= Chronic Lung Disease
PICU	= Pediatric Intensive Care Units
KFUH	= King Fahd University Hospital
IAU	= Imam Abdulrahman bin Faisal University
OI	= Oxygenation Index
OSI	= Oxygenation Saturation Index
CHD	= Congestive Heart Disease
CLD	= Chronic Lung Disease

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

The scientific research committee, the ethics committee at Imam Abdulrahman bin Faisal University (IAU), and the

ethical review board approved the study (IRB 2020-01-213).

HUMAN AND ANIMAL RIGHTS

This study didn't involve any animals. All human research protocols complied with the ethical norms of the institutional and national committees in charge of human testing and the Helsinki Declaration of 1975, as amended in 2013.

CONSENT FOR PUBLICATION

Patients approved using their records at admission for research purposes.

STANDARDS OF REPORTING

STROBE guidelines methodologies were followed in this study.

AVAILABILITY OF DATA AND MATERIALS

The authors confirm that the data supporting this study's conclusions are included in the paper.

FUNDING

None.

CONFLICT OF INTEREST

The authors have no conflicts of interest relevant to this article to disclose.

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