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Is Angiopiotin-2 Useful in Evaluation of Pediatric Patients with Sepsis?

Fady Mohamed El Gendy[1]; Thoria Ahmed Omar[2]; Fatma Abdelmohsen Abdelmageed[3]; Haidy Mohammed Zakaria[4]*; Alyaa Ahdy Abdel Aziz[1]

[1]Department of Pediatrics, Faculty of Medicine, Menoufia University, Menoufia Governorate, Egypt.

[2]Department of Clinical pathology, Faculty of medicine, Menoufia University, Menoufia Governorate, Egypt.

[3]Department of Pediatrics, Ashmoun general Hospital, Menoufia Directorate of Health Affairs, Ministry of Health and Population, Menoufia Governorate, Egypt.

[4]Department of Clinical Research and Health Development, Menoufia Directorate of Health Affairs, Ministry of Health and Population, 32511 Shebin El-Kom, Menoufia Governorate, Egypt.

***Corresponding Author(s): Haidy Mohammed Zakaria**
Department of Clinical Research and Health Development, Menoufia Directorate of Health Affairs, Ministry of Health and Population, 32511 Shebin El-Kom, Menoufia Governorate, Egypt.
Tel: +20-100-5768-306; E-mail: drhaydi2000@gmail.com

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Abstract

Background: Angiopoietin-2 has been used in adult patients for diagnosis of sepsis, prediction of sepsis severity and mortality. However, few studies have assessed its utility in pediatric sepsis.

Objective: to evaluate the utility of Angiopoietin-2 in diagnosis and prognosis of pediatric sepsis.

Methods: This is a prospective observational study conducted on two groups; patients group and control group. The patient group included 70 children admitted to the Pediatric Intensive Care Unit with diagnosis of sepis. The control group included 25 apparently healthy children. Patients were evaluated on admission by clinical examination, routine laboratory biomarkers and measurements of serum Angiopoietin-2 at 1st 24 hours of admission.

Results: the patients and controls were age and sex matched. The seventy septic cases were classified as sepsis 41(58.6%), severe sepsis 14(20%) and septic shock 15(21.4%). Twenty-six (37.1%) of cases has positive heamocultures. We found significant high levels of Angiopoietin-2 in cases versus controls with median (3000 pg/ml versus 277.5 pg/ml, respectively). No significant difference of Angiopoietin-2 between sepsis, severe sepsis and septic shock as the median and interquartile ranges (IQR) are 2300 (1775-3700), 3300 (2072.5-3850) and 2500 (1650-4100), respectively (P= 0.77). No significant difference between survivors and non-survivors regarding median and IQR of Angiopoietin-2 levels; 2750(1800-4012.5) versus 3050(1670-3550), P=0.67. Conversely, non survivors had significantly lower platelets count. Multivariate logistic regression analysis revealed that admission pSOFA, nosocomial infection and chronic complex conditions were independent predictor of mortality.

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Conclusion: Angiopoietin-2 is useful for diagnosis of pediatric sepsis but not for prognosis or prediction of mortality. Admission pSOFA, nosocomial infection and chronic complex conditions were more useful in that purpose.

Introduction

Sepsis is a pathology frequently encountered in pediatric intensive care units occurring as a major complication in the development of serious infections. Severe sepsis is defined as sepsis associated with organ dysfunction and associated with a high mortality rate and is caused by an infection induced immune response [1]. Although early prediction and proper management of septic patients is vital to reducing mortality, this can be difficult to achieve. In the early stage of sepsis, innate immunity is activated and subsequently ignites a cascade of immune responses within the cells [2]. The disorders of immunity function would lead to an autoamplifying cytokine production and eventually lead to organ dysfunction [3].

The definition remains vague because it is still challenging to describe the complex immune network system during the onset or progression of sepsis with a single biomarker. Diagnosis is based on clinical criteria, the principal indicator being a systemic inflammatory response syndrome (SIRS), triggered by an infection. The prognosis for these patients is dependent on the early establishment of the proper diagnosis and the quick initiate of antibiotic therapy [4].

Microvascular dysfunction is the endpoint of many life-threatening infections, and a well-established relationship exists between endothelial injury and sepsis [5]. Angiopoietin is part of a family of vascular growth factors that play a role in embryonic and postnatal angiogenesis. Angiopoietin cytokines are involved with controlling microvascular permeability, vasodilation, and vasoconstriction by signaling smooth muscle cells surrounding vessels[6].

Special attention has been given to new biomarkers associated with sepsis. Some of these have proved to be effective in in the diagnosis and prognosis of this severe disease. Angiopoietin-2 has been recently suggested as a robust predictor of severe sepsis during the early stages of infection and prior to the appearance of the clinical symptoms [7].

The aim of this study is to evaluate the utility of angiopoietin-2 in the diagnosis and prognosis of pediatric sepsis.

Patients and methods

This was a prospective observational study conducted on 70 children with a diagnosis of sepsis admitted into the Pediatric Intensive Care Unit (PICU) of Menoufia University Hospital and Ashmoun General Hospital, From October 2019 till December 2020 (Patient group) and 25 healthy controls (Control group).

Written informed consents were obtained from parents after explaining the aim of the study to them. Approval of the study was obtained from ethical committee of Faculty of Medicine, Menoufia University.

Patients with sepsis had undergone full history taking and thorough clinical examination. The admitting diagnosis and presence of any underlying illness were also noted, and the categorization of the admitting diagnosis was based on the organ affected by the primary diagnosis. Sepsis was diagnosed based on the International Pediatric Consensus Sepsis Conference (Goldstein et al., 2005) when the patient had two or more systemic inflammatory response syndrome (SIRS) criteria in association with proven or suspected infection. Pediatric Index of Mortality-2 (PIM2), and Pediatric Sequential Organ Failure Assessment (p-SOFA) score were calculated for all patients upon admission.

Patients investigated with routine investigations, C-Reactive Protein (CRP), Blood culture and measurement of serum angiopoietin-2 within 24 hours of PICU admission. X-ray, abdominal ultrasound and Computerized Tomography (CT) scan were done when needed.

Angiopoietin-2 was measured for both the patients and control groups. Serum Angiopoietin-2 was measured using commercial ELISA kits (Shanghai Sunred Biological Technology Co., Ltd., Shanghai, China).This assay employs the quantitative sandwich enzyme immunoassay technique. A monoclonal antibody specific for human Angiopoietin-2 has been pre-coated onto a microplate. Standards and samples are pipetted into the wells and any Angiopoietin-2 present is bound by the immobilized antibody. After washing away any unbound substances, an enzyme-linked monoclonal antibody specific for human Angiopoietin-2 is added to the wells. Following a wash to remove any unbound antibody-enzyme reagent, a substrate solution is added to the wells and color develops in proportion to the amount of Angiopoietin-2 bound in the initial step. The color development is stopped, and the intensity of the color is measured.

Statistical Analysis

Results were tabulated and statistically analyzed using Statistical Product and Service Solutions (SPSS) version 23, IBM SPSS Statistics for Windows, Armonk, NY: IBM Corp. The description of data was in the form of median (25th-75th) for quantitative data, and frequency and proportion for qualitative data. Mann-Whitney U test: was used to compare between two groups regarding non-normally distributed quantitative data. Kruskal-Wallis test: was used to compare between more than two groups in terms of non-normally distributed variable. Chi-Squared ($\chi 2$): It is used to compare qualitative variables between two or more groups. Univariate and Multivariate logistic regression analysis were used for prediction of mortality by different clinical and laboratory variables. Correlation coefficient test (Spearman correlation) was used to test the significance for correlation between two non-normally distributed quantitative variables. The ROC (receiver operating characteristic) curves was used to assess the performance of different variables in predicting the specified outcomes, including the optimal cut-offs, sensitivity and specificity. Results were considered significant if P-value ≤ 0.05.

Results

Both cases and controls were sex, age, weight and height matched (P>0.05). The median age in cases was16 months and in controls was 18 months. Males represented 44.3% of cases and 38.9% of controls. The median weight was 8.3 and 10.5 Kg in cases and controls respectively. Median height was 75.5 and 75 cm in cases and controls respectively.

Sepsis was the dominant group in our study (58.6%) followed by septic shock (21.4%) then severe sepsis (20%). Forty-seven percent of cases had chronic complex conditions, 34.3%of cases had shock at admission, 42.9% needed mechanical ventilation and few cases had acute respiratory distress syndrome (ARDS) (12.9%). Incidence of multiple organ dysfunction syndromes (MODS) at day 1, day 3 was 28.6% and 21.4%, respectively.

PIM2 mortality risk% and pSOFA scores had a median of 2.3 and 6 respectively, 25.7% of case had nosocomial infection and 37.1% of cases had positive blood culture. Mortality rate in our study was 34.3%. The values of different inflammatory and organ function markers are shown in **(Table 1)**.

Angiopoietin-2 showed significant high levels in cases than controls with median 3000 and 277.5 pg/mL, respectively **(Table 2)**. Angiopoietin-2 at cutoff value ≥ 725 pg/mL could discriminate patients with sepsis from controls with both sensitivity and Specificity of 100% (P <0.001, AUC = 1).

On comparing Angiopoietin-2 level according to illness severity; there was no significant difference in Angiopoietin-2 levels between the three categories of sepsis P-value = 0.77. Also, no significant difference in Angiopoietin-2 levels between patients on vasoactive medications and others, patients with ARDS and those who without, who are mechaniclly ventilated or not, who developed MODS on day 1 or day 3 also there's no significant difference in Angiopoietin-2 levels between cases who developed nosocomial infection and who didn't **(Table 2)**.

On comparing demographic, clinical data and laboratory data of patients according to sepsis severity; that mechanical ventilation had statistically significant correlation with sepsis severity. Vasoactive medications, vasopressor score at day 1 and vasopressor score at day 2 are statistically significant with sepsis severity as septic shock patients needed vasoactive medications with high scores. Also, MODS on day 1 and day 3 are statistically significant with sepsis severity as in septic shock it represent 66.7% and 53.3 %respectively. Severe sepsis group had the longest PICU stay with median 11.5 days. Both PIM2 and pSOFA score are significantly higher in severe sepsis and septic shock groups. Mortality is significantly higher in septic shock group (73.3%). The septic shock group has statistically significant lower platelet count, lower albumin levels and higher creatinine levels. No significant difference between the three groups regarding the other variables. No significant difference in Angiopoietin-2 between the three groups **(Table 3)**.

Angiopoietin-2 had no significant correlation with the patients' age, height, weight, PIM 2, pSOFA, vasoactive infusion days, CRP and platelet count, ventilator free days, vasopressor inotrope score at day 1, vasopressor inotrope score at day 2, vasoactive infusion days, mechanical ventilation duration, ventilator-free days, PICU stay, PIM2, pSOFA, or the laboratory paeameterts (P >0.05).

Concerning mortality, , no significant difference was found in Angiopoietin-2 level between survivors and non-survivors **(Table 2)**. Factors affecting patients' mortality were assessed; non–survivors had significantly higher frequency of septic shock, mechanical ventilation, MODS, complex chronic condition, nosocomial infections and ARDS compared with survivors. Mechanical ventilation duration, vasoactive infusion days, vasopressor scores, PIM2 and pSOFA score were also significantly higher among non- survivors. In addition; non-survivors had significantly lower platelet count **(Table 4)**.

Univariate logistic regression analysis for prediction of mortality showed that, pSOFA, mechanical ventilation, nosocomial infections, ARDS, chronic complex condition, vasopressor scores and low platelet count were positively associated with mortality, While the Multivariate logistic regression for predic-

Table 1: Demographic, clinical and laboratory data of the patients group.

Variable	Patients (n= 70)
	median (25^{th}-75^{th})
Age (months)	16 (5 – 60)
Weight (Kg)	8.3 (5.5 – 13.6)
Height (cm)	75.5 (62 – 95)
PIM2 mortality risk%	2.3 (1.6 – 5.8)
pSOFA	6 (5 – 9)
Mechanical ventilation duration (days)	0 (0 – 5)
Ventilator-free days	5 (3 – 9)
PICU stay (days)	7 (5 – 12.3)
Vasactive infusion days	0 (0 – 2)
Vasopressor inotrope score, day 1	0 (0 – 10)
Vasopressor inotrope score, day 2	0 (0 – 6.3)
Hemoglobin (g/dL)	10.2 (9.4 – 11.2)
WBCs (1000/uL)	15 (8.4 – 20.9)
ANC (1000/uL)	9.2 (4.9 – 14.1)
Platelets (1000/uL)	312 (158.3 – 377.5)
Creatinine (mg/dL)	0.6 (0.4 – 0.8)
Albumin (g/dL)	3.5 (3.1 – 3.9)
ALT (U/L)	24 (16 – 48.8)
CRP (mg/dL)	24 (6 – 66)

ALT: Alanine Transferase; ANC: Absolute Neutrophil Count; ARDS: Acute Respiratory Distress Syndrome; CRP: C-Reactive Protein; PELOD: Pediatric Logistic Organ Dysfunction Score, PICU: Pediatric Intensive Care Unit; PIM2: Pediatric Index Of Mortality2; PRISM: Pediatric Risk Of Mortality; SIRS: Systemic Inflammatory Response Syndrome; SOFA: Pediatric Sequential Organ Failure Assessment Score; WBCs: White Blood Cells.

Table 2: Comparison of the Angiopoietin-2 level between both patients and control groups, survivors and non-survivors and the different illness severity grades and markers.

Variable	Angiopoietin-2 (pg/mL)	P-value
	Median (25^{th}-75^{th})	
Patients (n=70)	3000 (1750 – 3762.5)	<0.001*
Controls (n=25)	277.5 (248.8 – 320)	
Survivors (n=46)	2750 (1800 – 4012.5)	0.67
Non-survivors (n=24)	3050 (1675 – 3550)	
Sepsis (n=41)	2300 (1775 – 3700)	0.77
Severe sepsis (n=14)	3300 (2072 – 3850)	
Septic shock (n=15)	2500 (1650 – 4100)	
Vasoactive medications	3000 (1875 – 3600)	0.96
No vasoactive medication	3000 (1750 – 3900)	
ARDS	3000 (1875 – 3250)	0.48
No ARDS	3000 (1750 – 4025)	
Mechanical ventilation	3050 (1750 – 3600)	0.98
No mechanical ventilation	2400 (1762 – 4037)	
MODS, day1	3350 (1875 – 4325)	0.13
No MODS	2300 (1750 – 3637.5)	
MODS, day 3	3300 (1650 – 4100)	0.86
No MODS	2500 (1787.5 – 3762.5)	
Nosocomial infections	3300 (1750 – 3737)	0.42
No nosocomial infections	2500 (1762 – 3787)	

Table 3: Demographic, clinical data and laboratory data of patients according to sepsis severity.

Variable	Sepsis (n=41)	Severe sepsis (n=14)	Septic shock (n=15)	P-value
Age (months)	12 (3.5 – 48)	17 (8 – 42)	24 (4 – 120)	0.46
Male sex	17 (41.5%)	6 (42.9%)	8 (53.3%)	0.73
Weight (Kg)	8.7 (5.1 – 13.5)	8 (6.5 – 11.8)	8.6 (6.5 – 25)	0.53
Height (cm)	67 (61 – 92.5)	75.5 (63.8– 88.3)	82 (71 – 125)	0.29
Complex chronic condition	19 (46.3%)	8 (57.1%)	6 (40%)	0.64
ARDS	3 (7.3%)	3 (21.4%)	3 (20%)	0.22
Mechanical ventilation	8 (19.5%)	12 (85.7%)	10 (66.7%)	<0.001*
Ventilator-free days	7 (4.5 – 10)	4.5 (2 – 9.5)	1 (0 – 5)	<0.001*
Nosocomial infections	9 (22%)	5 (35.7%)	4 (26.7%)	0.59
Vasoactive infusion days	0 (0 – 0)	0 (0 – 5.8)	4 (0 – 5)	<0.001*
Vasopressor-inotrope score (day 1)	0 (0 – 0)	0 (0 – 10)	10 (0 – 30)	<0.001*
Vasopressor-inotrope score (day 2)	0 (0 – 0)	0 (0 – 10)	20 (0 – 30)	<0.001*
MODS (day1)	3 (7.3%)	7 (50%)	10 (66.7%)	<0.001*
MODS (day 3)	2 (4.9%)	5 (35.7%)	8 (53.3%)	<0.001*
PICU stay (days)	8 (5 – 14)	11.5 (6.8 – 19.3)	5 (4 – 7)	<0.001*
PIM2 mortality risk%	1.8 (1.4 – 2.5)	7.5 (2.2 – 13.5)	4.8 (1.8 – 35.6)	<0.001*
pSOFA	5 (4 – 6)	8.5 (6 – 10.3)	10 (8 – 15)	<0.001*
Mortality	6 (14.6%)	7 (50%)	11 (73.3%)	<0.001*
CRP (mg/dL)	24 (9.2 – 57.5)	39 (12.3 – 84)	12 (0 – 80)	0.47
Hemoglobin (g/dL)	10.2 (9.6 – 11.1)	10.3 (8.4 – 11.9)	9.8 (8.8 – 11.5)	0.67
ANC (1000/uL)	8.6 (5.4 – 13.5)	10.8 (5.1 – 15)	8.7 (1.6 – 16.1)	0.63
WBC (1000/uL)	15 (9.2 – 20.7)	14.8 (10 – 19.9)	10.7 (4.8 – 21.9)	0.94
Platelets (1000/uL)	360 (196 – 432.5)	237 (157.8 – 344.3)	180 (82 – 337)	0.005*
Creatinine (mg/dL)	0.5 (0.4 – 0.6)	0.5 (0.3 – 1.4)	0.9 (0.7 – 1.8)	0.005*
ALT (U/L)	23 (17 – 34)	41 (18.4 – 156.5)	18 (15 – 54)	0.13
Albumin (gm/dL)	3.6 (3.5 – 3.9)	3.4 (2.3 – 3.8)	2.7 (2.2 – 3.4)	0.032*
Angiopoietin-2 (pg/ml)	2300 (1775–3700)	3300 (2072.5–3850)	2500 (1650–4100)	0.77

Quantitative data were presented as median (25^{th}-75^{th}), qualitative data were presented as number and (%)

Table 4: Demographic, clinical data and laboratory data of survivors and non-survivors.

Variable	Survivors (n=46)	Non-survivors (n=24)	P-value
Age, month	12 (4 – 48)	18 (5.8 – 111)	0.29
Male sex	20 (43.5%)	11 (45.8%)	0.85
Weight, Kg	8.7 (5.5 – 13.1)	8 (6.1 – 19.3)	0.52
Height, cm	71 (61 – 92.3)	79.5 (65.8 – 115.8)	0.096
Category			
Sepsis	35 (76.1%)	6 (25%)	<0.001*
Severe sepsis	7 (15.2%)	7 (29.2%)	
Septic shock	4 (8.7%)	11 (45.8%)	
Complex chronic condition	17 (37%)	16 (66.7%)	0.018*
ARDS	2 (4.3%)	7 (29.2%)	0.006*
Mechanical ventilation	9 (10.6%)	21 (87.5%)	<0.001*
MV duration	0 (0 – 0)	5 (2 – 12)	<0.001*
Nosocomial infections	6 (13%)	12 (50%)	0.001*
Vasoactive infusion days	0 (0 – 0)	4 (0 – 6)	<0.001*
Vasopressor-inotrope score (day 1)	0 (0 – 0)	10 (0 – 23.8)	<0.001*

Vasopressor-inotrope score (day 2)	0 (0 – 0)	15 (0 – 30)	<0.001*
MODS (day1)	6 (13%)	14 (58.3%)	<0.001*
MODS (day 3)	2 (4.3%)	13 (54.2%)	<0.001*
PICU stay, days	7 (5 – 12)	7.5 (4.3 – 22.8)	0.62
PIM2 mortality risk%	2.2 (1.6 – 3)	4.9 (1.5 – 19.2)	0.023*
pSOFA	5.5 (4.8 – 7)	9.5 (5.3 – 14.3)	<0.001*
CRP (mg/dL)	24 (7.8 – 52.5)	32 (6 – 87.5)	0.72
Hemoglobin (g/dL)	10.3 (9.6 – 11.3)	9.95 (8.8 – 10.8)	0.29
ANC (1000/uL)	8.9 (5.9 – 13.5)	9.9 (2.3 – 16.1)	0.97
WBC (1000/uL)	15.7 (9.9 – 20)	13.1 (4.1 – 22.4)	0.52
Platelets (1000/uL)	349.5 (175.5 – 424.5)	210.5 (82.8 – 346.5)	0.024*
Creatinine (mg/dL)	0.55 (0.4 – 0.7)	0.65 (0.5 – 1.3)	0.15
ALT (U/L)	21 (15 – 39.3)	26.5 (18 – 99.5)	0.13
Albumin (gm/dL)	0 (0 – 3.7)	2.1 (0 – 3.3)	0.73
Angiopoietin-2 (pg/ml)	2750 (1800 – 4012.5)	3050 (1675 – 3550)	0.67

Table 5: Logistic regression analysis for prediction of mortality by different variables.

Variable	Univariate analysis		Multivariate analysis	
	Odds ratio (95% CI)	p-value	Adjusted odds ratio (95% CI)	p-value
ARDS	9.1 (1.7 – 48)	0.01*	4.3(0.33-55.4)	0.27
Admission pSOFA	1.48 (1.19 – 1.84)	<0.001*	1.4 (1.1 – 1.9)	0.012*
Nosocmial infection	6.7 (2.1 - 21.6)	0.002*	7.8 (1.8 – 38.9)	0.012*
Mechanical ventilation	28.8 (7 – 118)	<0.001*	NA	NA
Complex chronic condition	3.4 (1.2 – 9.6)	0.021*	5.9 (1.2 – 30.1)	0.032*
Severe sepsis	9.5 (3 – 30)	<0.001*	4.6 (0.8 – 25.2)	0.082
Vasopressor-inotrope score (day 1)	1.1 (1.03 – 1.18)	0.004*	NA	NA
Vasopressor-inotrope score (day 2)	1.09 (1.04 – 1.15)	0.001*	NA	NA
Platelet count (on admission)	0.996 (0.993 – 1)	0.033*	NA	NA
Angiopoietin -2	1 (1 – 1)	0.74	NA	NA

tion of mortality showed that, pSOFA, nosocomial infections and chronic complex conditions were independent predictors of mortality. Also shows that Angiopoietin-2 levels had no relation in prediction of mortality **(Table 5)**.

Discussion

Sepsis and its related sequelae accounts for significant morbidity and mortality in critically ill children admitted to PICUs, So there's persistent need for early diagnosis and management to limit its serious outcomes. So many biomarkers used for diagnostic and prognostic utilities. One of these markers is Angiopoietin-2 which is an endothelial biomarker for sepsis and its sequelae which seems to be promising marker.

Here in, Our study results revealed significant increase in serum levels of angiopoietin-2 in our samples collected through 24 hours of admission in PICU in children diagnosed as sepsis, severe sepsis and septic shock more than healthy normal controls. Angiopoietin-2 at cut off point >725pg/ml could discriminate patients with and without sepsis with both sensitivity and Specificity of 100%. This result supports the hypothesis that angiopoietin-2 plays central role in the microvascular and endothelial dysfunction occurring in sepsis. Angiopoietin-2, an angiogenic peptide, activates endothelial cells and increases vascular inflammation. It functions as an autocrine mediator of the endothelium and is stored predominantly in endothelial cells [8].

Gulliano et al.,2014 who studied the kinetics of angiopoietins on admission and at 1st 4 days of admission; supported our results as they found that Angiopoietin-2 level was significantly higher in children admitted by sepsis, severe sepsis and septic shock than those without sepsis [9].

Despite the great difference in Angiopoietin-2 levels in cases and controls, Angiopoietin-2 levels were comparable among the different sepsis severity groups; sepsis, severe sepsis and septic shock. In addition; serum Angiopoietin-2 levels showed no correlation with severity scores represented in PIM 2 and pSOFA scores. Patients who needed mechanical ventilation and patients who did not, patients who developed ARDS and and patients who did not, even survivors and nonsurvivors had nearly comparable levels of Angiopoietin-2. So, Angiopoietin-2 is a good diagnostic not prognostic marker in patients with sepsis.

Despite that, other pediatric studies demonstrated that high Angiopoietin-2 levels is positively correlated with the severity of sepsis. Melendez et al., 2019 declared that there's significant elevation of serum Angiopoietin-2 in patients with septic shock than those with sepsis (P=0.008). They also demonstrate that Angiopoietin-2 levels correlated well with PRISM3 score but not with PELOD score at 24 hours [10]. Agrawal et al.,2012 found the relation between serum Angiopoietin-2 and development

of acute lung injury (ALI) and need for mechanical ventilation is statistically significant [11]. Calfee et al., 2012 revealed that higher levels of Angiopoietin-2 predict development of ARDS in critically ill patients. In a logistic regression model, Angiopoietin-2 alone significantly predicted the development of ALI [12].

In the current study, Angiopoietin-2 serum levels did not differ significantly between patients who received vasoactive medications and those who didn't. In addition; there was no correlation between serum Angiopoietin-2 and Vasopressor inotrope score at day 1 and day 2 or vasopressor infusion days although Szederjesi et al.,2015 demonstrated that, Angiopoietin-2 serum levels were correlated with the number of patients who required vasoactive treatment (P=0.043). However, they did not find significant correlation between Angiopoietin-2 levels and the number of days on vaso-active medication (P=0.465) [13].

In our study we noticed that; the increase in sepsis severity was associated with increase in the need for mechanical ventilation, vasoactive medications consumption and the length of PICU stay, but not with mortality outcome as in previous pediatric studies Who reported that PICU stay was affected by severity of sepsis but not an independent factor of mortality [14]. Hermon et al.,2021 found that there was no significant difference in the duration of PICU stay between the different age subgroups or between the different diagnoses or mortality outcome [15].

The admission hypoalbuminemia was significantly associated to sepsis severity as admission hypoalbuminemia was remarkable in septic shock. Previous pediatric study [16] found that the patients with hypoalbuminemia had higher delta neutrophil index, C-reactive protein, lactate level, PIM 3, PRISM III, 28-day mortality rate, incidence of septic shock, and lower hemoglobin level and platelet level compared to the normoalbuminemia patients in both infection and non-infection group but not associated with mortality outcome. (Lakkappa and Penta,2018) and (xu et al.,2020) reported a significant association between mortality and the level of albumin in the critically ill children [17,18].

Other neonatal studies showed that thrombocytopenia was observed in 58.7% of culture proven neonatal sepsis. Initial thrombocytopenia was common among Gram negative sepsis and mostly of a moderate degree in Candida sepsis (Bhat et al.,2018) and (Ree et al.,2017), thrombocytopenia in neonatal sepsis increases the risk of mortality nearly four-fold, with another six-fold increase in mortality in case of Gram-negative sepsis [19,20].

The mortality rate of our patients was 34,4% which is higher than in developed countries whose mortality rate around 25 % in PICUs [21,22], may be because of delays in presentation and/or diagnosis which are known risk factors for poor outcomes in limited resource settings, inappropriate treatment or delay administrating of antimicrobial agents and lack of diagnostic facilities.

About 66.7 %of deaths had chronic complex conditions which is an independent factor of predicting which is consistent with other pediatric studies as (Prout et al.,2018) who reported that More than 2 out of 3 children admitted with sepsis have at least 1 chronic disease and these patients have a higher in-hospital mortality than previously healthy patients. The burden of sepsis in hospitalized children is highest in pediatric patients with chronic disease. They reported that most deaths (68.6%) had a chronic disease. The in-hospital mortality was 3.7% overall; 0.7% for previously healthy patients and 5.1% for patients with chronic disease. In multivariable analysis, oncologic, hematologic, metabolic, neurologic, cardiac and renal disease, and solid organ transplant were associated with increased in-hospital mortality [23]. Ames et al.,2018 reported that notable factors associated with a statistically significant increased odds of death included diagnostic coding of septicemia; neurologic, cardiovascular, hematologic/immunologic, malignancy or neonatal-related chronic complex conditions; as well as presence of respiratory failure, liver failure or neurologic dysfunction on admission [24].

In our study septic shock represented 45.8% of deaths, de Souza and Machado,2019 reported that mortality is high in patients with septic shock, ranging from 5% in developed countries to up to 35% in developing countries [25]. Several studies in both developed and developing countries have shown that mortality from septic shock is associated with suboptimal care: delayed diagnosis and treatment and nonadherence to the treatment guidelines [26,27,28].

The ARDS represented 29.2 % of our which is consistent with Yadav et al.,2019 study, Who reported that Pediatric ARDS contributes to a significant burden in the PICU of a developing country and is associated with significantly higher mortality [29].

About 50% of deaths in our study had nosocomial infection which was a significant predictor of mortality. Pérez et al., reported that nosocomial infection was independent risk factors for increased mortality with OR 9.2, P=0.004 [30]. Murni et al.,2019 reported that the mortality is attributable to nosocomial bloodstream infection. An increased risk of death in children with nosocomial blood stream infection can be identified by simple clinical predictors including malnutrition, admission to the PICU and use of a central line catheter. Nosocomial blood stream infection was associated with increased mortality with an adjusted OR of 8.5 (95% CI 6.0–12.1). In multivariate analysis, malnutrition, admission to the PICU and use of a central line catheter were independently associated with an increased risk of death with adjusted ORs (95% CI), respectively, of 6.0 (1.6-22.6), 3.2 (1.6-6.7) and 3.1 (1.1-8.7) [31].

Limitations of the present study include the small sample size. Further studies with a larger sample size are needed to properly assess the diagnostic and prognostic roles of Angiopoietin-2 among pediatric patients with sepsis , also serial measurements of Angiopoietin-2 to fulfill its prognostic value in pediatric sepsis. Our current findings still show the diagnostic value of Angiopoietin-2. Further studies are required to establish the range of values for Angiopoietin-2 helping to further stratify patients into risk of mortality, and thereby tailoring care to individual case based level.

Whether Angiopoietin-2 is a marker of disease or one of the important etiologic factors in disease progression, remains unclear. In addition, although increased levels can give clues to possible mediators of the disease, they do not necessarily explain the mechanisms involved. Thus, if Angiopoietin-2 is a mere marker of endothelial dysfunction or a critical factor to the disease pathogenesis remains to be fully elucidated. In addition, Angiopoietin-2 could represent a promising candidate to develop novel therapeutic strategies against sepsis-induced vascular barrier breakdown.

Conclusion

Angiopoietin-2 is useful for confirming diagnosis of sepsis but not for outcome prediction.

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