Medical Oncology (2022) 39:6
https://doi.org/10.1007/s12032-021-01605-8

ORIGINAL PAPER

The role of inflammatory indices in the outcome of COVID-19 cancer patients

Hend A. Nooh[1] · Mona S. Abdellateif[2,6] · Lobna Refaat[1] · Eman Z. Kandeel[1] · Ahmed Bayoumi[3] · Mohamed Samra[4] · Medhat Khafagy[5]

Received: 20 September 2021 / Accepted: 27 October 2021 / Published online: 8 November 2021

Abstract

To assess the prognostic role of different inflammatory indices on the outcome of cancer patients with COVID-19. Sixty-two adults and 22 pediatric cancer patients with COVID-19 infection were assessed for the prognostic value of certain inflammatory indices including the neutrophil to lymphocyte ratio (NLR), monocyte to lymphocyte ratio (MLR), platelet to lymphocyte ratio (PLR), derived NLR (dNLR), systemic inflammation index (SII), mean platelet volume to platelet ratio (MPR), C-reactive protein to lymphocyte ratio (CRP/L), aggregate index of systemic inflammation (AISI), systemic inflammation response index (SIRI), and neutrophil to lymphocyte, platelet ratio (NLPR). Data were correlated to patients' outcome regarding ICU admission, and incidence of mortality. Increased CRP/L ratio in adult COVID-19 cancer patients was significantly associated with inferior survival [152 (19–2253) in non-survivors, compared to 27.4 (0.8–681) in survivors ($P=0.033$)]. It achieved a sensitivity (60%) and a specificity (90.2%) at a cut-off 152, while it achieved a sensitivity of 60% and specificity 95.1% at a cut-off 252 (AUC 0.795, $P=0.033$). When combining both CRP/L and NLPR for the prediction of poor outcome in adult cancer patients with COVID19, the sensitivity increased to 80% and the specificity was 70.7% (AUC 0.805, $P=0.027$). Increased incidence of ICU admission in pediatric cancer patients associated significantly with the severity of covid19 infection, decreased mean corpuscular hemoglobin (MCH) < 28.3, increased red cell distribution width (RDW) > 16, lymphopenia < 1.04, pseudo Pelger-Huet appearance, and PLR < 196.4 ($P=0.004$, $P=0.040$, $P=0.029$, $P=0.039$, $P=0.050$, and $P=0.040$; respectively). The mean corpuscular volume (MCV), MCH, and RDW could be useful prognostic markers for poor outcome in COVID-19 pediatric cancer patients ($P<0.05$ for all). Increased both CRP/L and NLPR associated significantly with poor survival in adult COVID-19 cancer patients, while PLR associated significantly with ICU admission in pediatric COVID-19 cancer patients.

Keywords COVID-19 · Inflammation index · Cancer · Pediatric · PLR · CRP/L and NLPR

✉ Mona S. Abdellateif
mona.sayed@nci.cu.edu.eg

[1] Clinical Pathology Department, National Cancer Institute, Cairo University, Cairo, Egypt

[2] Cancer Biology Department, National Cancer Institute, Cairo University, Cairo, Egypt

[3] Pediatric Oncology Department, National Cancer Institute, Cairo University, Cairo, Egypt

[4] Medical Oncology Department, National Cancer Institute, Cairo University, Cairo, Egypt

[5] Surgical Oncology Department, National Cancer Institute, Cairo University, Cairo, Egypt

[6] Medical Biochemistry and Molecular Biology, Cancer Biology Department, National Cancer Institute, Cairo University, Cairo, Egypt

Introduction

The pandemic of COVID-19 has become a worldwide healthcare problem, as it is responsible for about 62,773 deaths globally in the period between the end of 2019 and the 5th of April 2020 [1]. In fact, the COVID-19 pandemic is considered a life-threatening disease especially in patients who have comorbidities [2, 3]. Among them were the cancer patients, who are at a higher risk of developing adverse events including intensive care unit (ICU) admission, mechanical ventilation, and/or death more than patients without cancer [4]. Therefore, it is necessary for COVID-19 cancer patients to undergo special medical care, in addition, more research regarding the diagnosis and management is highly recommended to save these vulnerable patients.

It had been reported that most of COVID-19 patients have mild to moderate infection, while about 15–20% of cases develop severe form and require hospitalization, ICU admission, and/or mechanical ventilation [5–7]. A growing body of evidence indicates the important role of the inflammatory response accompanied by the virus infection, which is responsible for the pulmonary complications of COVID-19, that leads to acute respiratory distress syndrome (ARDS), and finally septic shock or multiple organ system failure (MOSF) [8, 9]. This inflammatory response is formed of uncontrolled production of inflammatory cytokines with the recruitment of inflammatory cells as macrophages and granulocytes that leads to cytokine storm [9, 10]. Peripheral white blood cell (WBC) count with its subtypes are good predictors for this systematic inflammatory response, and thereby the prognosis of the disease [10]. Many recently published studies demonstrated that many combined ratios of complete blood count (CBC) parameters such as NLR, dNLR, PLR, MLR, and SII could be useful diagnostic and prognostic markers for the severity of COVID-19 patients [11–13]. However, this situation would be different in cancer patients, as they have an incompetent immune system that is caused by either the nature of the cancer itself or the anticancer treatment [14, 15].

Therefore, the aim of the current study was to assess the prognostic role of different inflammatory indices including NLR, MLR, dNLR, PLR, SII, MPR, CRP/L, AISI, SIRI, and NLPR in cancer patients with COVID-19 infection. Data were correlated to the clinical features of both adult and pediatric cancer patients. As this may help to find an accurate, early, and accessible marker that could predict the prognosis and outcome of such COVID-19 cancer patients.

Patients and methods

This is a retrospective cohort study conducted on 84 pediatric and adult patients with different types of cancer and got COVID-19 infection. Those patients were admitted and treated at the National Cancer Institute (NCI) between June 2020 and March 2021. All patients were subjected to full history taking, full clinical examination, laboratory assessment in the form of complete hematological (Sysmex XN1000 and Sysmex XT1800) and coagulation profile, kidney function and liver function tests, serum Ferritin and D-dimer. Also, full radiological assessment especially chest X-ray and computed tomography (CT) on chest. Patients were proved to be COVID-19 positive based on the molecular, laboratory, and radiological findings according to the guidance of the world health organization (WHO) [16]. The adult cancer patients were assessed for the severity of SARS-COV-2 infection according to the WHO classification into; mild infection in patients with mild symptoms and normal imaging findings, moderate COVID-19 infection in patients with fever and lung affection by chest X-ray and CT, while severe infection in patients who had severe respiratory symptoms, respiratory rate > 30/min and O_2 saturation was < 93% in the rest state [16]. While pediatric cancer patients were classified according to the severity of SARS-COV-2 infection into asymptomatic infection in patients who had no symptom of COVID-19 at any time point, mild infection in patients who had mild symptoms and did not require hospitalization, moderate severity in patients who required inpatients management without ICU care, while severe infection in patients who required ICU care for COVID-19 symptoms [17].

Most of the patients 65/84 (77.4%) were receiving chemotherapy; 36 (42.9%) were on induction chemotherapy, 11 (13.1%) were on maintenance, and 8 (9.5%) patients were on consolidation chemotherapy. While the remaining 28 (33.3%) patients were post-surgery, and only one was receiving radiotherapy. In addition, there were 40 (47.6%) patients received intensified chemotherapy according to their risk stratification.

We tried to investigate the association between complete blood cell count (CBC)-derived different inflammatory indices and patients' outcome regarding ICU admission, and incidence of mortality, in both adult and pediatric COVID-19 cancer patients.

The inflammatory indices were calculated as follows: NLR (neutrophil/lymphocytes), MLR (monocyte/lymphocyte ratio), PLR (platelet/lymphocyte ratio), dNLR (neutrophils/(white blood cells − neutrophils)), MPR (mean platelet volume/platelet ratio), CRP/L (CRP/lymphocyte ratio), NLPR (neutrophil/(lymphocyte × platelet ratio)), SII ((neutrophils × platelets)/lymphocytes), AISI ((neutrophils × monocytes × platelets)/lymphocytes, and SIRI ((neutrophils × monocytes)/lymphocytes).

Statistical analysis

Data were analyzed using the SPSS package (version 22; SPSS Inc., Chicago, IL, USA). It was tested for normalization using Shapiro test. Continuous variables were expressed as median and interquartile range (IQR), while categorical variables were expressed as frequencies and percentages. Comparisons between groups were performed using Mann–Whitney test and Chi-square test for numerical and categorical variables, respectively. A receiver operating characteristic (ROC) curve analysis was performed to determine the ability of the inflammatory indices for association with mortality in adult and pediatric COVID-19 cancer patients. Univariate and multivariate regression analyses were performed to detect the prognostic value of the inflammatory indices regarding association with ICU admission in COVID-19 adult and pediatric cancer patients. All tests were

two-tailed and P value < 0.05 was considered a statistically significant.

Results

The current study included 84 cancer patients with COVID-19, 22 (26.1%) of them were pediatrics [50% (11/22) were male & 50% (11/22) were female], and 62 (73.8%) were adult patients [62.9% (39/62) were males and 37.1% (23/62) were females, $P = 0.320$]. Hematological malignancies were more common than solid tumors in pediatric patients [16 (72.7%) vs. 6 (27.3%); respectively], while solid tumors were more commonly observed in adults than hematological malignancies [35 (56.5%) vs. 27 (43.5%); respectively, $P = 0.025$]. The disease course was progressive in 72.6% (45/62) in adults compared to 68.2% (15/22) in pediatric cancer patients ($P = 0.785$).

The degree of COVID-19 infection in pediatric cancer patients was asymptomatic to mild in 7 (31.8%) patients, moderate in 5 (22.7%), and severe in 10 (45.5%) patients. While in adults, the degree of COVID-19 infection was mild in 26 (41.9%), moderate in 25 (40.3%), and severe in 11 (17.7%) patients, ($P = 0.033$). The ICU admission was encountered in 50% (11/22) of the pediatric patients, compared to 22.6% (14/62) of the adult patients ($P = 0.028$). There were 50% (11/22) of the pediatric cancer patients mechanically ventilated, compared to only 8.1% (5/62) of the adult patients ($P < 0.001$). Neutropenic sepsis was found in 9 (10.7%) patients [4/62 (6.5%) of adults, and 5/22 (22.7%) in pediatric patients, ($P = 0.049$)].

Of the adult patients, 14.5% (9/62) had one or more pre-existing diseases, including hypertension, cardiovascular disease, and diabetes, compared to only 9.1% (2/22) of pediatric COVID-19 cancer patients who had hypertension ($P = 0.575$). Finally, 40.9% (9/22) of pediatric patients, and 9.7% (6/62) of the adult patients died ($P = 0.002$). The other clinical features of the assessed patients were illustrated in Table 1.

Laboratory findings of the adult and pediatrics COVID-19 cancer patients

The morphological changes of the monocytes regarding being vacuolated, aggressive, and granular with cytoplasmic tail were significantly detected in pediatric patients ($P = 0.035$), where the monocytes' changes were positive in 19/22 (86.4%) and negative in 3/22 (13.6%). Meanwhile, in adult COVID-19 cancer patients, the monocytes' changes were positive in 38/62 (61.3%) and negative in 24/62 (38.7%). The acute phase reactants, e.g., Ferritin was increased in pediatrics than adults, but it did not reach a significant level [4337 (3610–6180) vs. 72 (10–135);

Table 1 Clinico-pathological features of the patients

Clinical variable	Patients		P value
	Pediatric (22)	Adult (62)	
Age			
Median (IQR)	11 (3–18)	44 (19–71)	< 0.001
Gender			
Male	11 (50%)	39 (62.9%)	0.320
Female	11 (50%)	23 (37.1%)	
Type of cancer			
Hematological malignancies	16 (72.7%)	27 (43.5%)	**0.025**
Solid tumors	6 (27.3%)	35 (56.5%)	
Disease status			
Remission	7 (31.8%)	17 (27.4%)	0.785
Stationary or progressed	15 (68.2%)	45 (72.6%)	
Degree of COVID infection			
Mild	7 (31.8%)	26 (41.9%)	**0.033**
Moderate	5 (22.7%)	25 (40.3%)	
Severe	10 (45.5%)	11 (17.7%)	
ICU admission			
Yes	11 (50%)	14 (22.6%)	**0.028**
No	11 (50%)	48 (77.4%)	
Mechanical ventilator			
Yes	11 (50%)	5 (8.1%)	**< 0.001**
No	11 (50%)	57 (91.9%)	
Death			
No	13 (59.1%)	56 (90.3%)	**0.002**
Yes	9 (40.9%)	6 (9.7%)	
Comorbidities			
No	20 (90.9%)	53 (85.5%)	0.575
HTN	2 (9.1%)	4 (6.5%)	
Cardiac disease	0 (0.0%)	4 (6.5%)	
DM	0 (0.0%)	1 (1.6%)	
Blood stream infection			
−ve	17 (77.3%)	57 (91.9%)	0.118
+ve	5 (22.7%)	5 (8.1%)	
Neutropenic sepsis			
No	17 (77.3%)	58 (93.5%)	**0.049**
Yes	5 (22.7%)	4 (6.5%)	
DCL			
No	18 (81.8%)	57 (91.9%)	0.232
Yes	4 (18.2%)	5 (8.1%)	
Liver disease			
No	19 (86.4%)	55 (88.7%)	0.717
Yes	3 (13.6%)	7 (11.3%)	
Renal disease			
No	19 (86.4%)	56 (90.3%)	0.691
Yes	3 (13.6%)	6 (9.7%)	
Duration of hospital stay			
Median (IQR)	11 (0–42)	10 (0–30)	0.656
< 10 days	11 (50%)	33 (55.0%)	0.804
> 10 days	11 (50%)	27 (45.0%)	

Bold values indicate statistically significant

respectively, ($P=0.064$)]. Also, there was a significant difference between the pediatric and adult patients regarding the kidney functions laboratory tests including Urea [24 (12–54) vs. 31 (13–86); respectively, ($P=0.022$)] and Creatinine [0.55 (0.3–1.2) vs. 0.8 (0. 3–3.6); respectively, ($P<0.001$)]. The other different laboratory parameters including Total Leukocyte Count (TLC), Hemoglobin concentration (Hb), Mean Corpuscular Volume (MCV), Mean Corpuscular Hemoglobin (MCH), Red Cell Distribution Width (RDW), Neutrophil, lymphocytes, and monocytes absolute and relative values did not show any statistical difference between the assessed adult and pediatric patients' groups (Table 2).

Inflammatory indices in adult and pediatric COVID-19 cancer patients

The median NLR in pediatric patients was 1.889 (IQR 0.1–16.6), while in adults it was 2.838 (IQR 0–30.3, $P=0.345$). The median LMR in pediatric patients was 2.072 (IQR 0.1–18.5), and in adults was 2.550 (IQR 0.4–120, $P=0.274$). The median PLR in pediatric patients was 196.428 (IQR 4.4–2054.5), and in adults, it was 156

Table 2 Laboratory findings of the adult and pediatric COVID-19 cancer patients

Clinical variable	Patients		*P* value	Clinical variable	Patients		*P* value
	Pediatric (22)	Adult (62)			Pediatric (22)	Adult (62)	
TLC	5.3 (.49–12.7)	7.9 (.27–31)	0.068	MCV	83.9 (70–96.5)	84.9 (51–807)	0.749
Hb	10.3 (7.7–16)	10.9 (4.9–16.3)	0.791	MCH	28.3 (21.5–34.3)	28.2 (19.2–85.4)	0.891
RDW	16.2 (13.3–43.8)	15 (11.6–21.2)	0.338	Normoblast	0 (0–1.3)	0 (0–1.3)	0.126
Platelet count	225 (31–724)	284(5–666)	0.583	MPV	10 (7.6–11)	10.3 (6.6–13.1)	0.284
Neutrophil	1.9 (.04–10.9)	4.9 (.03–28.6)	0.54	Neutrophil%	47.9 (7–86)	65 (11–92.4)	0.241
IG	0.02 (0.02–0.53)	0.04 (0.01–1.4)	0.650	IG%	0.6 (0.2–18.7)	0.5 (0.1–22.1)	0.107
Lymphocytes	1.04 (.12–2.86)	1.7 (0.09–4.4)	0.109	Lymphocytes%	21.1 (6.9–53.7)	20.5 (3–85.3)	0.734
Monocytes	0.58 (.04–1.79)	0.73 (.02–4.2)	0.263	Monocytes%	7.9 (0.8–71.9)	8.6 (1.7–34.5)	0.089
Eosinophil	0.03 (0–1.4)	0.09 (0–0.56)	0.192	Basophil	0 (0–2)	0 (0–0.06)	0.247
Giant				Blasts			
Negative	10 (45.5%)	21 (33.9%)	0.441	Negative	20 (90.9%)	52 (83.9%)	0.724
Positive	12 (54.5%)	41 (66.1%)		Positive	2 (9.1%)	10 (16.1%)	
Toxic granulation				Pelger-huet			
Negative	15 (68.2%)	38 (61.3%)	0.617	Negative	8 (36.4%)	20 (32.3%)	0.795
Positive	7 (31.8%)	24 (38.7%)		Positive	14 (63.6%)	42 (67.7%)	
Hypogranulation				Shift to left			
Negative	20 (90.9%)	55 (88.7%)	0.774	Negative	18 (81.8%)	45 (72.6%)	0.568
Positive	2 (9.1%)	7 (11.3%)		Positive	4 (18.2%)	17 (27.4%)	
Mature				Plasmoid			
Negative	3 (13.6%)	10 (16.1%)	0.781	Negative	3 (13.6%)	13 (21.0%)	0.543
Positive	19 (86.4%)	52 (83.9%)		Positive	19 (86.4%)	49 (79.0%)	
Monocytoid & Ballerina				Vacuolated, aggressive, monocovicyte			
Negative	8 (36.4%)	27 (43.5%)	0.621	Negative	3 (13.6%)	24 (38.7%)	**0.035**
Positive	14 (63.6%)	35 (56.5%)		Positive	19 (86.4%)	38 (61.3%)	
LDH	221 (127–762)	237 (129–1890)	0.990	Albumin	3.4 (1.9–4.2)	3.2 (1.8–4.6)	0.534
D-Dimer	0.5 (0–123)	4 (1–95)	0.414	Ferritin	4337 (3610–6180)	72 (10–135)	0.064
CRP	22.9 (0–248)	42 (1.8–406)	0.212	Total bilirubin	0.45 (0.2–2.5)	0.45 (0.1–4.7)	0.842
AST	20.5 (9–42)	19 (9–275)	0.142	ALT	20 (8–52)	21 (6–280)	0.951
Urea	24 (12–54)	31 (13–86)	**0.022**	Creatinine	0.55 (.3–1.2)	0.8 (0.3–3.6)	**< 0.001**
PT	1.12 (1–4.1)	1.14 (0.96–1.9)	0.849				

Bold values indicate statistically significant

The *P* value is significant if < 0.05

ALT alanine transaminase, *AST* aspartate transaminase, *CRP* C- reactive protein, *Hb* hemoglobin concentration, *IG* immature granulocyte, *LDH* lactate dehydrogenase, *MCH* mean corpuscular hemoglobin, *MCV* mean corpuscular volume, *MPV* mean platelet volume, *PT* prothrombin time, *RDW* red cell distribution width, *TLC* total leukocyte count

(IQR 2.7–2322.2, $P=0.101$). The median d(NLR) in pediatric patients was 0.8878 (IQR 0.08–9.50), and in adults it was 1.5874 (IQR 0–12.07 $P=0.203$). The median SII index in pediatric patients was 291.64 (IQR 1–8154), and in adults it was 615.98 (IQR 0–9752, $P=0.303$). The median CRP/L in pediatric patients was 55.84 (IQR 0–998.33), and it was 30.92 (IQR 0.79–2253.3, $P=0.985$) in adults. The median MPR in pediatric patients was 0.0437 (IQR 0.01–0.35), and it was 0.0342 (IQR 0.01–0.45, $P=0.384$) in adults. The median NLPR in pediatric patients was 0.0107 (IQR 0–0.07), and in adults was 0.0114 (IQR 0–0.35, $P=0.726$). The median SIRI in pediatric patients was 0.61 (IQR 0–20.16), while in adults was 1.516 (IQR 0–23.56, $P=0.146$). The median AISI in pediatric patients was 98.58 (IQR 0–1459.9), while it was 289.51 (IQR 0–8821.9, $P=0.091$) in adult COVID-19 cancer patients (Fig. 1).

Association between inflammatory indices and the outcome of the assessed COVID-19 cancer patients

Patients were categorized according to their outcome regarding ICU admission and mortality.

Increased CRP/L ratio in adult COVID-19 cancer patients was significantly associated with inferior survival, as it was 152 (19–2253) in non-survivors, compared to 27.4 (0.8–681) in survivors ($P=0.033$). Other inflammatory indices showed no statistical difference between ICU admitted/non admitted patients nor survivors/non-survivors COVID-19 cancer patients (Table 3).

Regarding COVID-19 pediatric cancer patients, the association between inflammatory indices and patients' outcome showed no statistically significant difference between ICU admitted pediatric patients and non-ICU patients. Also, there were no significant differences between survivors and non-survivors in pediatric COVID-19 cancer patients (Table 4).

The ROC curve analysis of inflammatory indices showed that CRP/L associated significantly with increased mortality in adult COVID-19 cancer patients with a sensitivity of 60% and a specificity of 90.2% at a cut-off 152, while it achieved a sensitivity of 60% and specificity 95.1% at a cut-off 252 (AUC 0.795, $P=0.033$, Fig. 2). While, when combining both CRP/L and NLPR for the prediction of the poor outcome in adult COVID19 cancer patients, the sensitivity increased to 80% and the specificity was 70.7% (AUC 0.805, $P=0.027$, Table 5). However, ROC analysis did not reveal any statistical significance of the assessed other inflammatory indices for predicting mortality in either adult or pediatric COVID-19 cancer patients (Figs. 2 and 3).

Univariate analysis of risk factors for COVID-19 associated ICU admission in cancer patients

Increased incidence of ICU admission in pediatric cancer patients associated significantly with increased severity of covid19 infection (OR 72, $P=0.004$), as out of the 11 patients who admitted to the ICU, 10 patients had severe COVID-19 infection. Also, increased incidence of ICU admission in pediatric cancer patients associated significantly with decreased MCH below 28.3 (O.R 7.11, $P=0.040$), increased RDW > 16 (OR 12, $P=0.029$). In addition, the degree of lymphopenia (lymphocytes < 1.04) associated significantly with poor prognosis (OR 1.77, $P=0.039$). Similarly, abnormality in neutrophils morphology with pseudo Pelger-Huet appearance associated with dismal outcome (OR 8, $P=0.050$). The PLR as an inflammatory index (< 196.4 vs > 196.4) significantly predicts poor patients' prognosis (OR 7.11, $P=0.040$, Table 6).

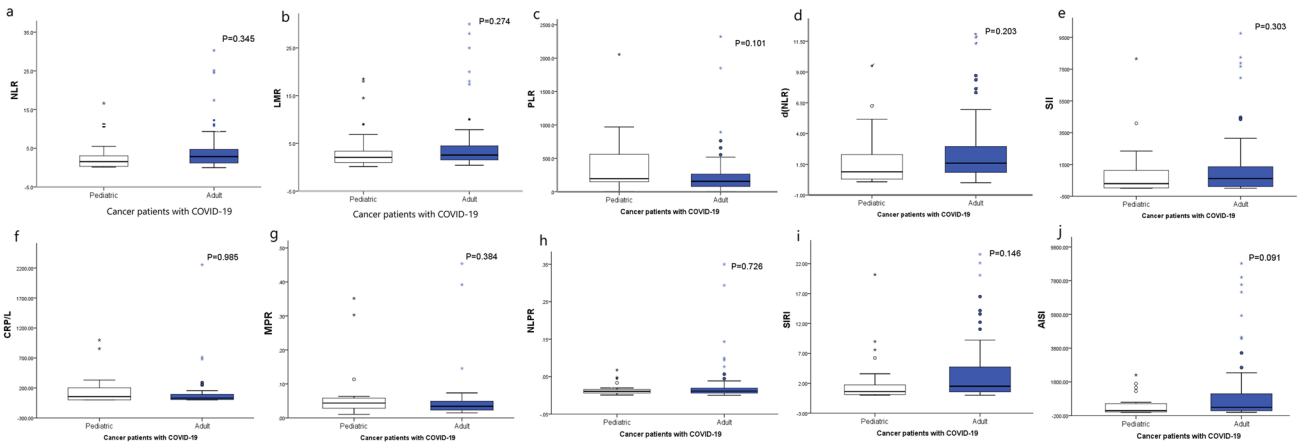

Fig. 1 Expression levels of different inflammatory indices (NLR, MLR, PLR, dNLR, SII, MPR, CRP/L, AISI, SIRI, and NLPR) in adult and pediatric COVID-19 cancer patients

Table 3 Association between inflammatory indices and patients' outcome in adult cancer patients with COVID-19

Index	ICU admission		*P* value	Death		*P* value
	Yes ($n=14$)	No ($n=48$)		Yes ($n=6$)	No ($n=56$)	
NLR	4.8 (1.7–24.5)	3.3 (0–25.1)	0.957	2.99 (0.2–24.5)	3.2 (0–30.3)	0.437
LMR	2.6 (0.9–10)	2.5 (0.4–20)	0.204	1.7 (0.8–18)	2.5 (0.4–25)	0.910
PLR	241 (81–2322)	161 (5–519)	0.722	128 (3.4–386.7)	167 (5–2322)	0.821
dNLR	2.8 (1.2–11.3)	2.1 (0.12–11.8)	0.762	1.1 (0.16–11.3)	2.1 (0.12–12.1)	0.192
SII	1301 (446–7878)	704 (0–6946)	0.423	570 (1–7878)	754 (0–9752)	0.281
CRP/L	27.8 (2–289)	23.9 (0.8–250)	0.278	152 (19–2253)	27.4 (0.8–681)	**0.033**
MPR	0.03 (0.01–0.05)	0.04 (.02–1.96)	0.072	0.0 (0.03–0.03)	0.04 (.01–1.96)	0.595
NLPR	0.01 (0–0.08)	0.01 (0–1.7)	0.915	0.04 (0–0.08)	0.01 (0–1.7)	0.408
SIRI	2.9 (0.2–23.6)	2 (0 -20.1)	0.845	12 (0.5–23.6)	2 (0 -20.1)	0.802
AISI	1211 (39–7960)	501 (.01–8822)	0.557	3866 (169–7963)	501 (.01–8822)	0.341

Bold value indicates statistically significant

The *P* value is significant if <0.05

AISI aggregate index of systemic inflammation, *CRP/L* C-reactive protein to lymphocyte ratio, *dNLR* derived neutrophil to lymphocyte ratio, *MLR* monocyte to lymphocyte ratio, *MPR* mean platelet volume to platelet ratio, *NLPR* neutrophil to lymphocyte, platelet ratio, *NLR* the neutrophil to lymphocyte ratio, *PLR* platelet to lymphocyte ratio, *SII* systemic inflammation response index, and *SIRI* systemic inflammation response index

Table 4 Association between inflammatory indices and patients' outcome in pediatric cancer patients with COVID-19

Index	ICU admission		*P* value	Death		*P* value
	Yes ($n=11$)	No ($n=11$)		Yes ($n=9$)	No ($n=13$)	
NLR	2.9 (0.2–11.3)	2 (0.3–10.6)	0.718	2.9 (0.2–11.3)	2 (0.3–10.6)	0.973
LMR	1.9 (0.5–3.1)	1.4 (0.3–3.4)	0.768	1.9 (0.5–3.1)	1.4 (.3–3.4)	0.713
PLR	176 (9.5–862)	604 (119–970)	0.250	176 (9.5–862)	604 (119–970)	0.713
dNLR	2 (0.1–3.6)	0.5 (0.2–6.2)	0.974	2 (0.1–3.6)	0.5 (0.2–6.2)	0.973
SII	863 (7–8154)	302 (119–2344)	0.718	863 (7–8154)	302 (119–2344)	0.920
CRP/L	2.9 (0.8–203)	54.8 (0–332)	0.600	2.9 (0.79–203)	54.8 (0–332)	0.223
MPR	0.03 (0.01–0.35)	0.05 (0.03-.06)	0.560	0.03 (0.01–0.35)	0.05 (0.03-.06)	0.674
NLPR	0.01 (0–0.02)	0.01 (0–0.05)	0.250	0.01 (0–0.02)	0.01 (0–0.05)	0.243
SIRI	1.5 (0.12–20)	0.72 (0.07–7.6)	0.870	1.5 (0.12–20)	0.72 (0.07–7.6)	0.764
AISI	492 (9–14,594)	139 (24–1687)	0.718	492 (9–14,595)	140 (24–1688)	0.973

The *P* value is significant if <0.05

AISI aggregate index of systemic inflammation, *CRP/L* C-reactive protein to lymphocyte ratio, *dNLR* derived neutrophil to lymphocyte ratio, *MLR* monocyte to lymphocyte ratio, *MPR* mean platelet volume to platelet ratio, *NLPR* neutrophil to lymphocyte, platelet ratio, *NLR* the neutrophil to lymphocyte ratio, *PLR* platelet to lymphocyte ratio, *SII* systemic inflammation response index, and *SIRI* systemic inflammation response index

However, univariate analysis for COVID-19 associated ICU admission in adult cancer patients revealed that disturbed conscious level (DCL) associated significantly with inferior outcome of the patients (OR 11.1, $P=0.046$). The other clinicopathological features assessed did not show any significant difference (Table 7).

The prognostic role of RBCs indices in COVID-19 cancer patients

The ROC analysis was performed to evaluate the role MCV, MCH, and RDW in predicting the outcome in COVID-19 cancer patients. It showed that the sensitivity, specificity,

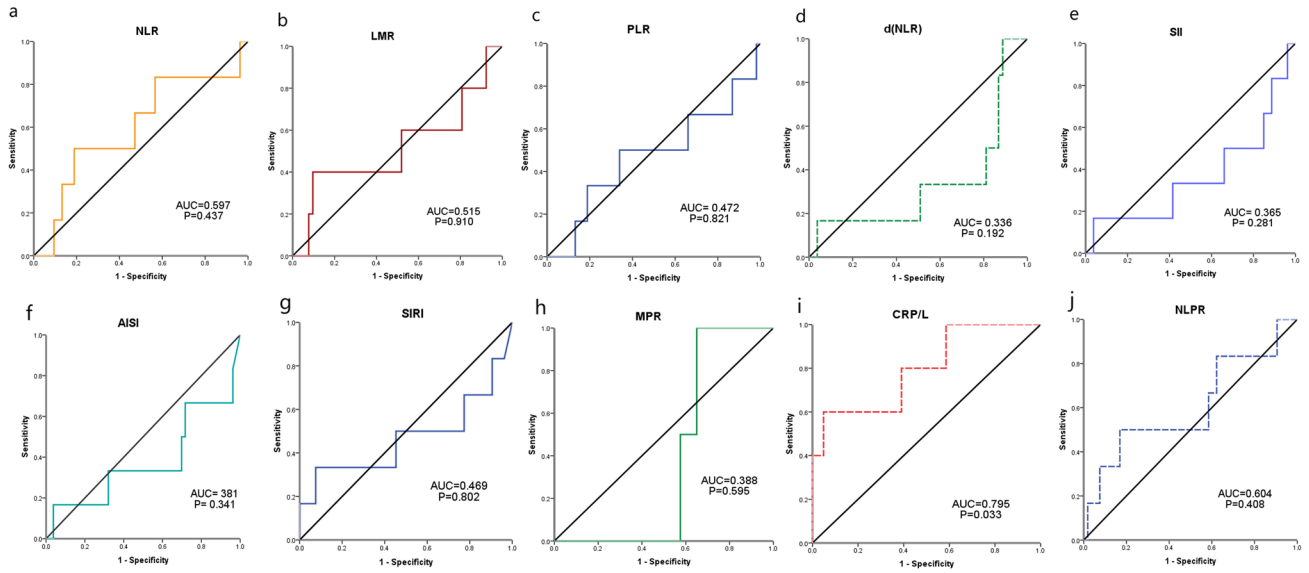

Fig. 2 ROC curve analysis of inflammatory indices (NLR, MLR, PLR, dNLR, SII, AISI, SIRI, MPR, CRP/L, and NLPR) for association with mortality in adult COVID-19 cancer patients

Table 5 ROC curve analysis of inflammatory indices for association with mortality in adult cancer patients

	AUC	Cut-off	Sensitivity (%)	Specificity (%)	*P* value
CRP/L	0.795	152	60	90.2	**0.033**
	0.795	252	60	95.1	
NLPR	0.604	0.028	50	83	0.408
CRP/L + NLPR	0.805	–	80	70.7	**0.027**

Bold values indicate statistically significant

and AUC of MCV were 90%, 100%, and 0.926; respectively, ($P=0.001$), at a cut-off (83.6 fL), MCH were 81.8%, 72.7%, and 0.802; respectively, ($P=0.017$), at a cut-off (27.7 Pg), and the RDW were 72.7%, 90%, and 0.841; respectively, ($P=0.008$) at a cut-off (16.3 fL), for association with increased incidence of ICU admission in pediatric COVID-19 cancer patients (Fig. 4A–C). Where the mean Hb concentration for these children was 9.9 ± 2.5 gm/dl. While for increased mortality rates, the sensitivity, specificity, and AUC of MCV were 88.9%, 92.3%, and 0.889; respectively, ($P=0.002$), at a cut-off (84.4 fL), MCH were 77.8%, 61.5%, and 0.752; respectively, ($P=0.049$) at a cut-off (27.7 Pg), and for RDW, they were 77.8%, 83.3%, and 0.778; respectively, ($P=0.033$) at a cut-off (16.3 fL, Fig. 4E–G). Regarding the combination of MCV, MCH, and RDW together in pediatric COVID-19 cancer patients, it showed a sensitivity (81.8%), specificity (100%), AUC (0.927) for association with ICU admission ($P=0.001$, Fig. 4D), and the mean Hb concentration for these children was 10.4 ± 2.5 gm/dl. While it achieved a sensitivity (77.8%), specificity (83.3%), AUC (0.843) for association with increased incidence of mortality ($P=0.009$, Fig. 4H). However, these parameters did not show any significant association with the outcome of adult COVID-19 cancer patients (data not shown).

Discussion

Many studies have reported the useful diagnostic and prognostic roles of different inflammatory indices in COVID-19 infection in noncancer population [11–13]; however, their role in COVID-19 cancer patients is not well assessed. In the current study, we could not find any significant impact of NLR, MLR, dNLR, SII, MPR, AISI, and SIRI on the outcome of both adult and pediatric cancer patients with COVID-19 infection, which was in contrast to that observed in COVID-19 non-cancer patients [18–20]. Meanwhile, other studies demonstrated that increased levels of NLR, PLR, and SII associated significantly with death in patients with lung, bladder, and cervical cancer [21–23]. This discrepancy in the results could be explained by that cancer patients with COVID-19 viral infection have underlying risk factors regarding the type of cancer, as well as the type of treatment, e.g., chemotherapy, radiotherapy, or cytotoxic drugs with their known myelosuppressive and immunosuppressive consequences [24]. As this myelosuppressive and/or immunosuppressive effect causes reduction in the neutrophil, monocyte, platelets, RBCs, T-cell, and B-cell populations [25], which affects their derived inflammatory indices. Therefore, it will eventually elucidate a different response to

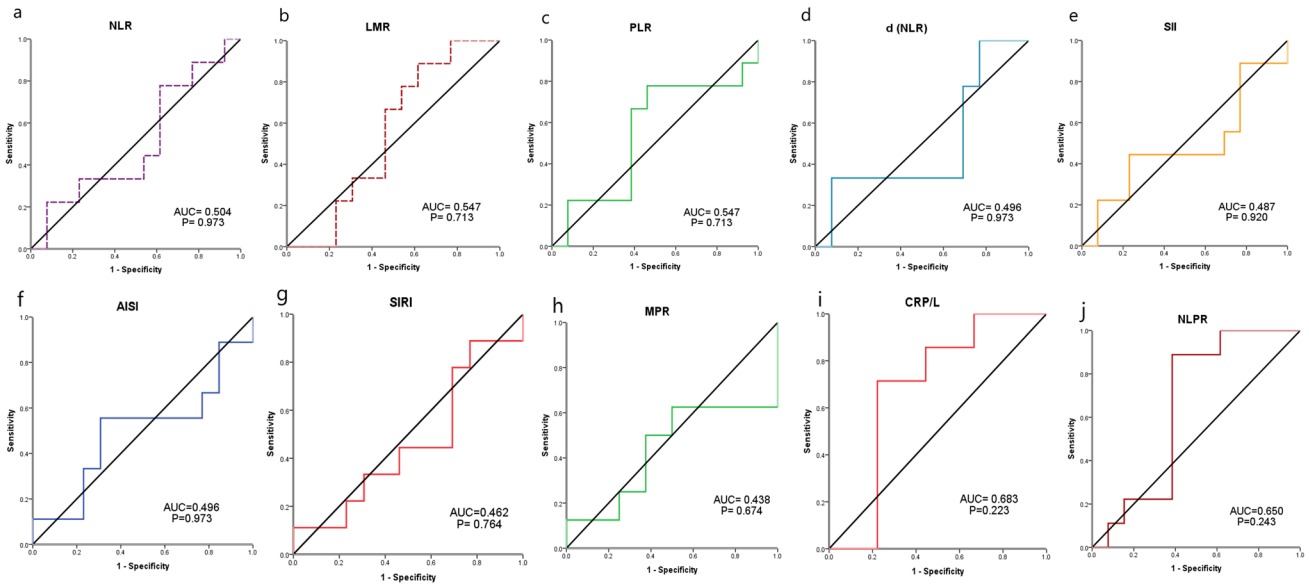

Fig. 3 ROC curve analysis of inflammatory indices (NLR, MLR, PLR, dNLR, SII, AISI, SIRI, MPR, CRP/L, and NLPR) for association with mortality in pediatric cancer patients

the COVID-19 infection or its treatment, unlike in COVID-19 non-cancer patients.

Moreover, many recent series reported that cancer patients infected with COVID-19 had more severe outcomes compared to those noncancer COVID-19 patients, especially in those with hematological or lung malignancies [24, 26]. Mehta et al. demonstrated increased case fatality rate (CFR) in cancer patients with COVID-19 infection, it was 37% for hematologic malignancies and 25% for solid tumors. They proposed this high CFR in cancer patients with COVID-19 might be due to the presence of co-morbidities associated with cancer patients, or due to the myelosuppressive effect of the anticancer treatment received. Moreover, they also concluded that COVID-19 infection could increase the risk of mortality regardless of the cancer type [24].

The present study demonstrated that increased CRP/L ratio was the only index associated significantly with lower survival in adult COVID-19 cancer patients. Furthermore, these data were confirmed by the ROC curve analysis which showed that CRP/L associated significantly with increased mortality in adult COVID-19 cancer patients with a sensitivity of 60% and a specificity of 90.2% at a cut-off 152, and the specificity increased to 95.1% at a cut-off 252. While, when combining both CRP/L and NLPR for the prediction of the poor outcome in adult COVID19 cancer patients, the sensitivity increased to 80% and the specificity was 70.7% (AUC 0.805). Therefore, increased both CRP/L and NLPR could be useful prognostic markers for the prediction of poor outcome in adult COVID-19 cancer patients. These data are in agreement with many recent reports concluded that decreased lymphocyte to C-reactive protein ratio is considered a predictor factor for poor outcome and mortality in COVID-19 patients [19, 27, 28]. The CRP is an inflammatory marker that synthesized in the liver, and it is considered an important inflammatory marker for bacterial infection [28]. In addition, it responds to the inflammatory cytokines produced by the activated monocytes or macrophages after infection [29]. Hence, the serum level of CRP could reflect the severity of inflammation and consequently the cytokine storm associated with COVID-19 severity [30–32]. Though, the increased serum level of CRP is normally lacking in viral infection, Paces and his colleagues tried to explain this phenomenon in their review. They proposed that the association of increased serum level of CRP with COVID-19 severity is attributed to the development of the macrophage activation syndrome together with the increased production of interleukin-6, which are responsible for the deterioration of the COVID-19 patients [33].

In contrary to our results, Lee et al. [34], investigated the hematological and biochemical parameters prior to and during coronavirus disease 2019 in cancer patients. They found that higher neutrophil count and higher NLR were significantly associated with increased mortality. This difference could be explained by the small number of patients included in the current study (84 patients) compared to 302 patients recruited in their study. However, in line with the present data, they could not find a significant impact of disease stage, neutropenia or lymphopenia on COVID-19 adult cancer patients' outcomes. Though these findings are contradictory to that observed by Feng et al. [35], in their meta-analysis, that increased neutrophil count and lymphopenia ($< 1 \times 10^9$/l) associated with the severity of COVID-19

Table 6 Bivariable regression models of potential prognostic variables associated with ICU admission in COVID-19 pediatric cancer patients

	Odds ratio	95% CI		*P* value
		Lower	Upper	
Gender male vs female	2.917	0.442	19.234	0.266
Disease (progression vs remission)	1.500	0.189	11.927	0.702
Degree of COVID-19 (sever vs moderate or mild)	72.000	3.841	1349.547	**0.004**
DCL (+ve vs −ve)	3.429	0.287	40.946	0.330
Blood stream infection (+ve vs −ve)	1.500	0.189	11.927	0.702
Comorbidities (+ve vs −ve)	2.000	0.150	26.734	0.600
Liver disease (+ve vs −ve)	2.000	0.150	26.734	0.600
Type of cancer Hematological vs solid	2.000	0.250	15.991	0.513
TLC (< 10 vs > 10)	2.000	0.150	26.734	0.600
Hb (< 10 vs > 10)	1.867	0.283	12.310	0.517
MCV (< 90 vs > 90)	.000	.000		0.999
MCH (< 28.3 vs > 28.3)	7.111	1.089	46.441	**0.040**
RDW (> 16 vs < 16)	12.000	1.294	111.323	**0.029**
NRBC (< 1 vs > 1)	.000	0.000		0.999
PLTs (> 150 vs < 150)	2.000	0.312	12.840	0.465
MPV (< 10 vs > 10)	2.667	0.347	20.508	0.346
Giant (+ve vs −ve)	1.250	0.205	7.615	0.809
Neutrophil > 7.5 vs < 7.5	2.000	0.150	26.734	0.600
Neutrophil < 70 vs > 70	1.143	0.126	10.386	0.906
Toxicgran (+ve vs −ve)	1.333	0.204	8.708	0.764
Pelger-huet (+ve vs −ve)	8.000	1.001	63.963	**0.050**
Hypogranulation (+ve vs −ve)	.000	.000		0.999
Shift to left (−ve vs +ve)	2.571	0.192	34.473	0.476
IGRc(1)	2.000	0.134	29.808	0.615
Lymphocyte (< 1.04 vs > 1.04)	1.77	56.123	1.105	**0.039**
Lymphocyte % (> 21.1 vs < 21.1)	5.4	0.088	0.778	37.505
Mature (+ve vs −ve)	0.500	0.037	6.683	0.600
Plasmoid (+ve vs −ve)	0.500	0.037	6.683	0.600
Monocytoid (+ve vs −ve)	1.333	0.204	8.708	0.764
Monocyte (< 1 vs > 1)	3.429	0.287	40.946	0.330
Monocyte % (< 10 vs > 10)	1.200	0.194	7.441	0.845
Vacuolated (+ve vs −ve)	2.571	0.192	34.473	0.476
PT (> 1 vs < 1)	3.333	0.384	28.959	0.275
CRP (> 6 vs < 6)	1.905	0.340	10.667	0.464
LDH (> 220 vs < 220)	2.519	0.460	13.801	0.287
Albumin (< 3.5 vs > 3.5)	3.000	0.562	16.013	0.199
ALT (< 55 vs > 55)	6.545	0.541	79.232	0.140
AST (< 34 vs > 34)	1.937	0.396	9.491	0.415
Total bilirubin (< 1.2 vs > 1.2)	2.000	0.146	27.447	0.604
Ceartnin (< 1.25 vs > 1.25)	1.500	0.241	9.345	0.664
Urea (< 45 vs > 45)	1.212	0.212	6.935	0.829
NLR (< 1.89 vs > 1.89)	1.440	0.269	7.721	0.675
LMR (> 2.07 vs < 2.07)	1.400	0.256	7.714	0.670
PLR (< 196.4 vs > 196.4)	7.111	1.089	46.441	**0.040**
dNLR (> 0.89 vs < 0.89)	3.062	0.539	17.401	0.207
SII (> 291.6 vs < 291.6)	1.440	0.269	7.714	0.670
CRP/L (< 55.8 vs > 55.8)	2.778	0.367	21.029	0.323

Table 6 (continued)

	Odds ratio	95% CI		*P* value
		Lower	Upper	
MPR (> 0.044 vs < 0.044)	1.667	0.227	12.221	0.615
SIRI (> 0.61 vs < 0.61)	1.440	0.269	7.714	0.670
AISI (> 98.5 vs < 98.5)	1.440	0.269	7.714	0.670
NLPR (< 0.012 vs > 0.012)	3.062	0.539	17.401	0.207

Bold values indicate statistically significant

The *P* value is significant if < 0.05

AISI aggregate index of systemic inflammation, *ALT* alanine transaminase, *AST* aspartate transaminase, *CRP* C- reactive protein, *CRP/L* CRP to lymphocyte ratio, *dNLR* derived neutrophil to lymphocyte ratio, *Hb* hemoglobin concentration, *IG* immature granulocyte, *LDH* lactate dehydrogenase, *MCH* mean corpuscular hemoglobin, *MCV* mean corpuscular volume, *MLR* monocyte to lymphocyte ratio, *MPR* mean platelet volume to platelet ratio, *MPV* mean platelet volume, *NLPR* neutrophil to lymphocyte, platelet ratio, *NLR* the neutrophil to lymphocyte ratio, *PLR* platelet to lymphocyte ratio, *PT* prothrombin time, *RDW* red cell distribution width, *SII* systemic inflammation response index, and *SIRI* systemic inflammation response index, *TLC* total leukocyte count

infection in non-cancer patients. However, the explanation could be that cancer patients already had lymphopenia prior to infection with COVID-19, which is responsible for lack of significant association with the COVID-19 severity. Also, it made cancer patients liable for more severe COVID-19 infection and poorer outcome rather than non-cancer patients [34]. In addition to the presence of neutropenic sepsis which contributed to the neutropenia encountered in our cohort of cancer patients. On the other hand, regarding the recruited pediatric cancer patients, children with lymphopenia ($< 1.04 \times 10^9$/l) were significantly at a higher risk for ICU admission 1.77 times more than in COVID-19 pediatric cancer patients who had lymphocytes more than 1. 04×10^9/l. This finding indicates that there is a difference between children and adults regarding both innate and adaptive immune responses [36, 37]. Moreover, in this issue, Dong et al. [38], demonstrated in their study that children are more prone to respiratory infections, and thus may have higher levels of antibodies against the virus than adults, or that their developing immune systems may react to pathogens differentially than adult immune system.

It had been reported that children showed a different disease course for COVID-19 rather than in adults [39]. Despite the increasing number of pediatric cancer case with COVID-19 infection, little is known about the impact of the hematological and laboratory profiles on the outcome of these patients [40]. In this context, the present data showed that that there was no significant association between the assessed inflammatory indices and the outcome of COVID-19 pediatric cancer patients, except for the PLR. Children with PLR lower than 196.4 were significantly 7.1 times more liable for ICU admission rather than those who had PLR > 196.4. As PLR is considered as an indicator of inflammation and cytokine storm, hence associated with the severity of COVID-19 infection, and consequently poor outcome [41].

Moreover, Increased incidence of ICU admission in pediatric cancer patients associated significantly with the severity of covid19 infection (OR 7), decreased MCH below 28.3, increased RDW > 16, lymphopenia (lymphocytes < 1.04), and presence of abnormality in neutrophils' morphology with pseudo Pelger-Huet appearance associated with dismal outcome. These data are consistent with Ma et al. [42] who concluded that lymphopenia and neutrophil abnormality could predict computed tomography (CT) results in pediatric COVID-19 patients. Similarly, other recently published studies reported the association of peripheral pseudo Pelger-Huet appearance and the severity of COVID-19 viral infection [43–45].

Interestingly, the present study demonstrated the important prognostic role of MCV, MCH, and RDW in predicting the outcome of pediatric COVID-19 cancer patients. As these markers (MCV < 83.6 fL, MCH < 27.7 Pg, and RDW > 16.3 fL) could possibly predict the incidence of ICU admission and/or death in these patients. Regarding the combination of MCV, MCH, and RDW together in pediatric COVID-19 cancer patients, it showed a sensitivity (81.8%), specificity (100%), and AUC (0.927) for association with ICU admission. While it achieved 77.8% sensitivity, 83.3% specificity, and AUC of 0.843 for association with increased incidence of mortality. However, these parameters did not show any significant association with the outcome of adult COVID-19 cancer patients. These data are partially comparable to that found by Wang et al. [46], who performed their study on adult non-cancer patients with COVID-19 infection, and reported that MCV and MCH were significantly lower in COVID-19 patients with poor outcome than in the good outcome group. Also, they reported that RDW was

Table 7 Bivariable regression models of potential prognostic variables associated with ICU admission in COVID-19 adult cancer patients

	Odds ratio	95% CI		*P* value
		Lower	Upper	
Gender (male vs female)	1.071	0.293	3.921	0.917
Disease (progression vs remission)	1.091	0.277	4.296	0.901
Degree of COVID-19 (sever vs moderate or mild)	3.254	0.808	13.753	0.088
DCL (+ve vs −ve)	11.100	1.039	118.566	**0.046**
Blood stream infection (+ve vs −ve)	3.273	0.412	26.014	0.262
Comorbidities (+ve vs −ve)	1.600	0.337	7.593	0.554
Liver disease (+ve vs −ve)	3.500	0.610	20.097	0.160
Renal disease (+ve vs −ve)	1.029	0.097	10.853	0.981
Type of cancer Solid vs Hematological	1.821	0.477	6.957	0.381
TLC (< 10 vs > 10)	1.648	0.458	5.928	0.444
Hb (< 10 vs > 10)	1.296	0.367	4.583	0.687
MCV (< 90 vs > 90)	6.094	0.758	55.732	0.095
MCH (< 28.2 vs > 28.2)	1.944	0.534	7.079	0.313
RDW (> 16 vs < 16)	1.179	0.317	4.384	0.806
NRBC (< 1 vs > 1)	1.091	0.103	11.527	0.942
PLTs (> 150 vs < 150)	1.358	0.313	5.897	0.683
MPV (< 10 vs > 10)	1.909	0.453	8.044	0.378
Giant (+ve vs −ve)	1.244	0.313	4.954	0.756
Blast (+ve vs −ve)	2.550	0.487	13.340	0.268
Neutrophil (< 7.5 vs > 7.5)	1.156	0.289	4.618	0.838
Neutrophil % (> 70 vs < 70)	1.432	0.369	5.551	0.604
Toxic granulation (+ve vs −ve)	2.424	0.573	10.252	0.229
Pelger-huet (+ve vs −ve)	3.214	0.841	12.283	0.088
Hypo-granulation (+ve vs −ve)	.471	0.070	3.194	0.441
Shift to left (−ve vs +ve)	2.538	0.485	13.279	0.270
Lymphocyte (> 3.5 vs < 3.5)	6.364	0.525	77.079	0.146
Lymphocyte % (> 35% vs < 35%)	1.051	0.266	4.145	0.944
Mature (+ve vs −ve)	2.550	0.487	13.340	0.268
Plasmoid (+ve vs −ve)	.805	0.145	4.476	0.804
Monocytoid (+ve vs −ve)	2.000	0.559	7.151	0.286
Monocyte (< 1 vs > 1)	1.571	0.287	8.595	0.602
Monocyte % (< 10 vs > 10)	1.600	0.371	6.906	0.529
Vacuolated (+ve vs −ve)	1.071	0.293	3.921	0.917
PT (> 1 vs < 1)	3.333	0.384	28.959	0.275
CRP (> 6 vs < 6)	1.905	0.340	10.667	0.464
LDH (> 220 vs < 220)	2.519	0.460	13.801	0.287
Albumin (< 3.5 vs > 3.5)	3.000	0.562	16.013	0.199
ALT (< 55 vs > 55)	6.545	0.541	79.232	0.140
AST (< 34 vs > 34)	1.937	0.396	9.491	0.415
Total bilirubin (< 1.2 vs > 1.2)	2.160	0.228	20.492	0.502
Ceartnin (< 1.25 vs > 1.25)	1.500	0.241	9.345	0.664
Urea (< 45 vs > 45)	.825	0.144	4.725	0.829
NLR (< 2.8 vs > 2.8)	1.524	0.455	5.109	0.495
LMR (> 2.55 vs < 2.55)	2.274	0.653	7.920	0.197
PLR (> 156 vs < 156)	1.524	0.455	5.109	0.495
dNLR (< 1.59 vs > 1.59)	1.045	0.315	3.470	0.942
SII (> 615.9 vs < 615.9)	1.524	0.455	5.109	0.495
CRP/L (> 30.9 vs < 30.9)	1.240	0.342	4.487	0.744

Table 7 (continued)

	Odds ratio	95% CI		*P* value
		Lower	Upper	
MPR (< 0.034 vs > 0.034)	3.000	0.655	13.747	0.157
NLPR (< 0.0114 vs > .0114)	1.524	0.455	5.109	0.495
SIRI (> 1.52 vs < 1.52)	1.045	0.315	3.470	0.942
AISI (> 289.5 vs < 289.5)	1.045	0.315	3.470	0.942

Bold value indicates statistically significant

The *P* value is significant if < 0.05

AISI aggregate index of systemic inflammation, *ALT* alanine transaminase, *AST* aspartate transaminase, *CRP* C- reactive protein, *CRP/L* CRP to lymphocyte ratio, *dNLR* derived neutrophil to lymphocyte ratio, *Hb* Hemoglobin concentration, *IG* immature granulocyte, *LDH* lactate dehydrogenase, *MCH* mean corpuscular hemoglobin, *MCV* mean corpuscular volume, *MLR* monocyte to lymphocyte ratio, *MPR* mean platelet volume to platelet ratio, *MPV* mean platelet volume, *NLPR* neutrophil to lymphocyte, platelet ratio, *NLR* the neutrophil to lymphocyte ratio, *PLR* platelet to lymphocyte ratio, *PT* prothrombin time, *RDW* red cell distribution width, *SII* systemic inflammation response index, and *SIRI* systemic inflammation response index, *TLC* total leukocyte count

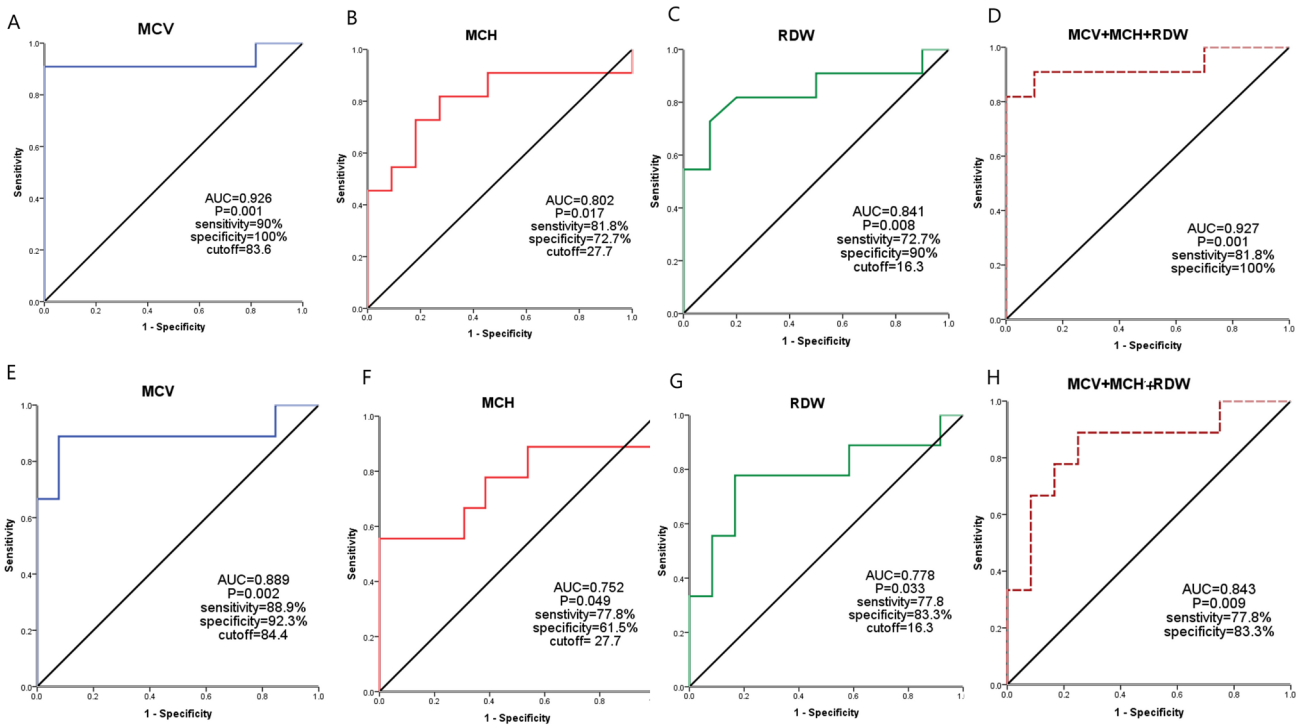

Fig. 4 ROC curve analysis of MCV, MCH, RDW and their combination for association with ICU admission (**A, B, C, D**) and increased incidence of mortality (**E, F, G, H**) in pediatric COVID-19 cancer patients

a prognostic predictor for patients with severe COVID-19 viral infection.

Taken together, we can conclude that cancer patients with COVID-19 have hematological and inflammatory indices different from that in COVID-19 non-cancer patients. Similarly, these inflammation indices are varied between pediatric and adult COVID-19 cancer patients. The increased level of both CRP/L and NLPR associated significantly with poor survival in adult COVID-19 cancer patients, while PLR associated significantly with ICU admission in pediatric COVID-19 cancer patients. Moreover, lymphopenia $< 1.04 \times 10^9$/l will significantly predict ICU admission. The possibility of the integration of those inflammatory indices in peripheral blood picture could be a very useful method for early prediction and prognosis of COVID19 cancer patients. As these indices are very easy and rapid

for calculations, as well as low-cost wise in low-income countries.

The MCV, MCH, RDW, and lymphopenia could be useful prognostic markers for poor outcome in COVID-19 pediatric cancer patients. However, these data should be verified on a larger number of patients including adult, pediatric, cancer, and non-cancer patients with COVID-19 infection for further confirmation.

Acknowledgements This work was supported by Cairo University, Fund No. 10/2020.

Declarations

Conflict of interest All authors declare that there is no possible conflict of interest.

Ethical approval The manuscript protocol had been approved by the institutional review board (IRB) committee of the National Cancer institute, which is in concordance with 2011 Declaration of Helsinki.

Informed consent A written informed consent had been obtained from all participant patients before inclusion in the study.

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