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ORIGINAL ARTICLE

Association between C-reactive protein levels and outcome in acute lung injury in children

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Abstract High plasma C-reactive protein (CRP) levels are associated with favorable outcome in adults with acute lung injury (ALI). The association between CRP levels and outcome has not been studied in ALI in children. We performed a historical cohort study in 93 mechanically ventilated children (0–18 years) with ALI. The CRP level within 48 h of disease onset was tested for association with 28-day mortality and ventilator-free days (VFD). Clinical parameters and ventilator settings were evaluated for possible confounding. Fourteen patients died within 28 days. The median (interquartile range) CRP level in nonsurvivors was 126 mg/L (64; 187) compared with 56 mg/L (20; 105) in survivors (p=0.01). For every 10-mg/L rise in CRP level, the unadjusted odds (95 % confidence interval (95 % CI)) for mortality increased 8.7 % (2.1–15.8 %). Cardiovascular organ failure at onset of ALI was the strongest predictor for mortality (odds ratio, 30.5 (6.2–152.5)). After adjustment for cardiovascular organ failure, for every 10-mg/L rise in CRP level, the OR (95 % CI) for mortality increased 4.7 % (−2.7–12.6 %; p=0.22). Increased CRP levels were associated with a decrease in VFD (ρ=−0.26, p=0.01). *Conclusion*: increased plasma CRP levels are not associated with favorable outcome in ALI in children. This is in contrast with findings in adults with ALI.

Keywords Acute lung injury · C-reactive protein · Child · Mechanical ventilation · Epidemiology · Biological markers

Abbreviation list

ALI	Acute lung injury
ARDS	Acute respiratory distress syndrome
CI	Confidence interval
CRP	C-reactive protein
CVOF	Cardiovascular organ failure
IQR	Interquartile range
OR	Odds ratio
PEEP	Positive end expiratory pressure
PICU	Pediatric intensive care unit
PRISM	Pediatric risk of mortality
VFD	Ventilator-free days

Introduction

Acute lung injury (ALI), in its severe form called acute respiratory distress syndrome (ARDS), is a life-threatening condition of pulmonary inflammation leading to severe oxygenation anomalies and respiratory distress [17]. Although children are less likely to develop ALI compared with adults, mortality in children may be as high as 35 % [5]. Risk factors for the development of ALI/ARDS in children are well established and seem to be similar to those in adults. They include both pulmonary and nonpulmonary conditions, such as sepsis, pneumonia, and aspiration [14, 17]. However, predictors of outcome of ALI are not alike in children and adults.

Recently, it has been shown that in adults with ARDS, high plasma C-reactive protein (CRP) levels predict a

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favorable outcome [1]. Paradoxically, CRP levels are generally used as a biomarker for systemic inflammation, and higher values are associated with adverse outcomes [8]. The association between CRP levels and outcome has not been investigated in children with ALI/ARDS. However, in children with meningococcal septic shock, low CRP levels are associated with fatal outcome, suggesting that in some diseases in childhood, high CRP levels do have an association with favorable outcome [10].

If we could establish an association between CRP level and outcome in ALI in children, we might extend our understanding of the differences and similarities in epidemiology between adults and children in ALI/ARDS. These epidemiological data might be a starting point to investigate differences in pathophysiology, such as differences in regulation of the inflammatory response in ALI/ARDS between adults and children. Less importantly, we might be able to more easily identify children at risk for severe outcomes in ALI, which could become of importance when new treatment modalities for ALI become available.

The aim of this study was to determine if increased plasma CRP levels are associated with favorable outcome in terms of 28-day mortality and ventilator-free days (VFDs) in children with ALI/ARDS.

Methods

We performed a historical cohort study in consecutive children aged 0–18 years who were mechanically ventilated >24 h at the pediatric intensive care unit (PICU) of the Emma Children's Hospital in Amsterdam from January 2008 through December 2009. This PICU is a 16-bed, tertiary care, multidisciplinary unit. All patient files were screened for the presence of ALI/ARDS between 24 and 72 h after the onset of mechanical ventilation using the criteria for ALI/ARDS set by the American European Consensus Conference [2]. Gas exchange criteria for ALI and ARDS were considered to be met if the PaO_2/FiO_2 ratio was less than 40.0 kPa for ALI and less than 26.7 kPa for ARDS in at least two consecutive measurements (>4 h apart). Exclusion criteria were: (1) gestational age of <40 weeks at onset of mechanical ventilation, (2) structural congenital malformations of the thorax or lungs, (3) noninvasive ventilation, or (4) chronic ventilation through a tracheal cannula. After consultation with the Institutional Review Board (MEC AMC, University of Amsterdam), the need for ethical approval was waived.

Data collection

The primary outcome measures were 28-day mortality and 28-day VFDs, defined as the number of days free of mechanical ventilation for survivors and zero for nonsurvivors [16]. Plasma CRP level, leukocyte count, clinical parameters, and mechanical ventilation settings at the time of fulfillment of the ALI/ARDS criteria were recorded. Plasma CRP level was considered to be missing if no measurement was performed at >24 h before or <48 h after onset of ALI/ARDS. Disease severity on admission was measured by the pediatric risk of mortality (PRISM) II score, which depends on diagnosis and clinical parameters in the first 24 h of admission [13]. Cardiovascular failure was defined as the need for vasoactive drugs.

Sample collection

Blood was routinely collected in ethylenediaminetetraacetic acid containing tubes, and CRP level was measured within 2 h after sampling using an immunoturbimetric assay (CRPL3, Roche Diagnostics GmbH, Mannheim, Germany).

Statistical analysis

Statistical analyses were performed using a statistical software program (PASW Statistics 18, Release 18.0.2 2010, SPSS Inc., Chicago). The comparability of patient characteristics for both groups was tested by means of a Chi-square test for dichotomous data and a Mann–Whitney *U* test for continuous data. The association between CRP level and 28-day mortality was investigated by logistic regression analysis. Potential confounders were identified by a >10 % difference in the regression coefficient (*B*) of CRP level between a logistic regression model containing only CRP and one in which with the potential confounder was added. The model with the largest explained variance based on the Nagelkerke R^2 was used to report the adjusted OR.

Spearman's correlation coefficient was calculated to evaluate the association between CRP level and VFDs. The effect of CRP level on mortality was also investigated by dichotomizing CRP levels using an arbitrarily defined, but clinically useful cut-off value of 100 mg/L [1].

We performed subgroup analyses in children with or without infection and in children who fulfilled the gas criteria for ARDS. Infection was defined as local or systemic inflammation caused by a proven or clinically suspected biological pathogen. Statistical significance was set at 5 %.

Results

In total, 369 patients were screened, of whom 36 were excluded and 14 had relevant information missing. Reasons for exclusion and an overview of patient selection are presented in Fig. 1. Of the remaining 319 patients, 98 patients developed ALI/ARDS of whom 14

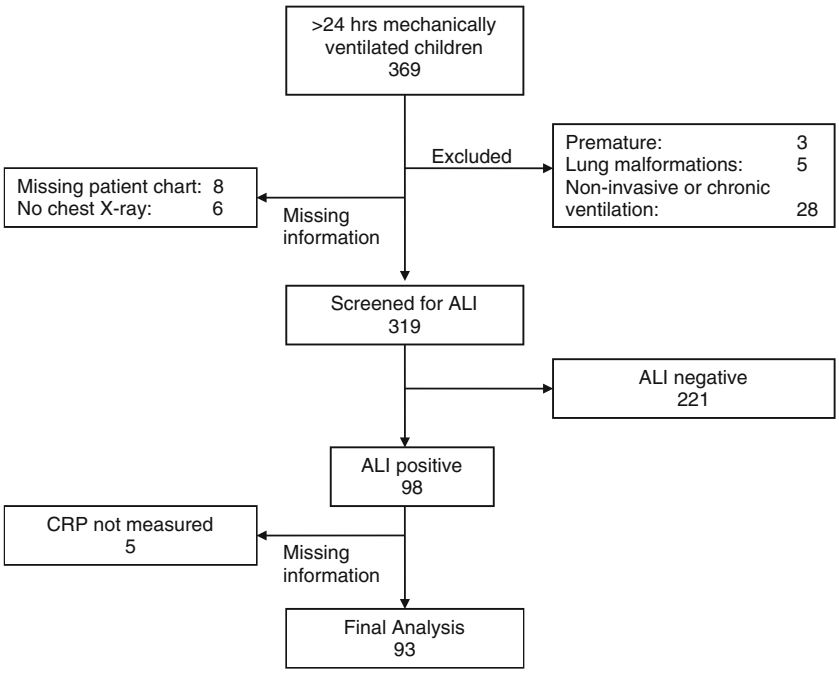

Fig. 1 Flowchart with reasons for exclusion and an overview of patient selection

died within 28 days. Plasma CRP level was measured in 93 patients. None of the five patients in whom no CRP level was measured died. Patient characteristics and a comparison between survivors and nonsurvivors are presented in Table 1.

Plasma CRP level and mortality

The median (interquartile range (IQR)) CRP level in nonsurvivors was 126 mg/L (64; 187) compared with 56 mg/L (20; 105) in survivors (p=0.01; Fig. 2). The results of the uni- and bivariable logistic regression analyses are presented in Table 2. Of all confounders, cardiovascular organ failure (CVOF) at onset of ALI was the strongest predictor for mortality. After adjustment for CVOF, for every 10 mg/L rise in CRP level, the odds for mortality increased 4.7 % (95 % confidence interval (95 % CI), −2.7–12.6 %; p=0.22).

In the subgroup analysis of children with ARDS (n=60), for every 10 mg/L rise in CRP level, the adjusted odds for mortality increased 5.6 % (95 % CI, −2.9–14.8%; p=0.20). Finally, in children with (n=64) and without infections (n=29), for every 10 mg/L rise in CRP level, the adjusted odds for mortality increased 4.0 (95 % CI, −4.2–12.8%; p=0.35) and 7.0 % (95 % CI, −8.3–24.7 %; p=0.39), respectively.

Plasma CRP level and VFDs

Increased CRP levels were weakly associated with a decrease in VFDs (Spearman's ρ, −0.26; p=0.01). The median (IQR) number of VFDs in children with a CRP level above 100 mg/L (n=31) was 20 (0; 23) compared with 23 (16; 24) in children with a CRP level of below 100 mg/L (n=62) at onset of ALI (p=0.02).

Other clinical variables and their association with 28-day mortality

In 60 children, ALI progressed to ARDS within 72 h. This was not associated with increased mortality (OR, 1.45 (95 % CI, 0.42–5.04)). The PRISM score was significantly associated with mortality (OR, 1.13 (95 % CI, 1.06–1.21)), as was age (in years; OR (95 % CI, 1.13 (1.03–1.12)).

Causes of death

ALI was identified as the cause of death in 2 of the 14 children who died. Seven children suffered from extensive brain damage and further treatment was considered futile. Other causes of death included shock (n=2) and hypoxia due to refractory pulmonary hypertension (n=2). One child died shortly after discharge from the PICU, the cause of death remained unclear.

Discussion

We did not show an association between increased plasma CRP levels in ALI in children and favorable outcome in terms of mortality and VFDs. In fact, we showed that increased CRP levels in ALI in children are weakly associated with a decrease of VFDs. However, this finding could

Table 1 Patient characteristics and comparison between survivors and nonsurvivors

Characteristics	Survivors (n=79)	Nonsurvivors (n=14)	p value
Demographic data			
Median age (months (range))*	6 (0, 213)	64 (2, 195)	0.004
Boys	48	12	0.072
Health status			
History of premature birth	14	4	0.344
History of chromosomal or metabolic disease	7	4	0.035
Pre-existing liver failure	0	0	n.a.
Etiology of ALI/ARDS			
Airway infection	55	3	<0.001
Aspiration	3	3	0.013
Sepsis	2	1	0.368
Postsurgery	8	0	0.213
Trauma	1	1	0.162
Leukemia	0	2	<0.001
Asthma	3	0	0.459
Status epilepticus	2	2	0.046
Other	5	2	0.314
Physiologic parameters			
Median PRISM score (range)*	11 (0, 32)	23 (5, 44)	0.003
ARDS within 72 h	50	10	0.558
Median leukocyte count (range)*	9.5 (0, 26)	10.2 (0, 47)	0.668
Cardiovascular failure	13	12	<0.001
Ventilation parameters at onset of ALI/ARDS			
Median tidal volume per kilogram bodyweight (mL (range))*	7.5 (2, 22)	8 (6, 10)	0.466
Median PEEP (range)*	6 (4,15)	7 (4,13)	0.210
Median PaO_2/FiO_2 ratio (range)*	22.0 (2, 39)	18.7 (9, 37)	0.442
Mechanical ventilation duration			
Median duration of mechanical ventilation (h (range))*	139 (40, 1,096)	134 (48, 527)	0.336
Median number of VFD (range)	23 (0, 27)	0	<0.001
Transferred to ECMO	1	1	0.162

ALI acute lung injury, *ARDS* acute respiratory distress syndrome, *PRISM* pediatric risk of mortality, *PEEP* positive end expiratory pressure, *VFD* ventilator-free days

*p values stated for Mann-Whitney U test. All other/non-marked p values stated for Chi-square tests. No missing values, with the exception of PRISM score (n=2) and leukocyte count (n=3)

not be adjusted for confounding and thus should be interpreted with caution.

The incidence of ALI in our cohort of ventilated children is higher than in most reports in literature [5, 18]. This might be explained by the fact that we only included children that were ventilated for >24 h and excluded those on noninvasive ventilation. Mortality in our cohort was low compared with some previous reports (8–62 %), but mortality in recent studies is comparable with our data [5, 6, 11, 14, 18]. Differences in mortality are very likely due to differences in the underlying diseases that triggered ALI. Therefore, despite our use of the international consensus, criteria defining ALI, the generalizability of our findings might be limited to PICUs with a comparable patient population and treatment of ALI. Heterogeneity in diseases underlying ALI is not only a concern in our study but in almost all studies in ALI in children, as outcome does depends on the underlying cause of ALI [9]. We included four children in which ALI occurred during mechanical ventilation for status epilepticus, which seems an unlikely cause of ALI. Nevertheless, in a recent survey of the incidence of ALI at a neurological ICU, the majority of patients with status epilepticus did fulfil ALI criteria [7].

To our knowledge, this is the first study investigating the predictive value of CRP levels in children with ALI/ARDS. Our results are in line with the majority of studies on the predictive value of CRP levels in other diseases [8, 15]. However, the results are in contrast with a recent finding in a cohort of adults with ARDS by Bajwa et al. [1]. In that study, the median CRP level in survivors was 176.5 mg/L compared with 133.5 mg/L in nonsurvivors. Bajwa et al. hypothesized that high CRP levels might reduce

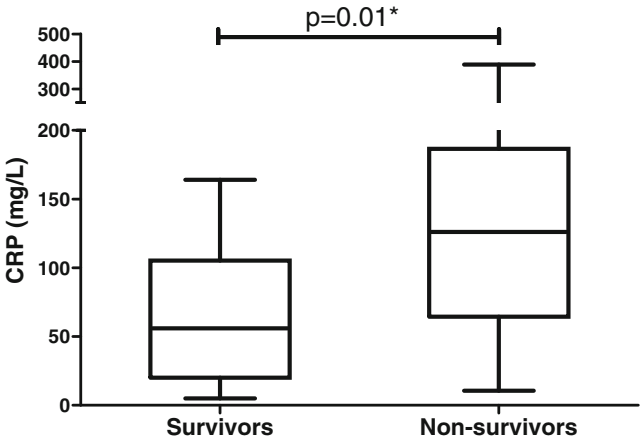

Fig. 2 Comparison of plasma C-reactive protein levels at onset of disease between survivors and nonsurvivors of pediatric acute lung injury. *p value stated for Mann-Whitney U test; vertical bars represent 10-90 % range

neutrophilic inflammation. In the context of our results, one could theoretically argue that this function of CRP does not exist in children. Alternatively, the findings of Bajwa et al., yet to be reproduced, might be a spurious finding. It is questionable if a single biomarker, like CRP, could be a reliable predictor of outcome in a multifactorial disease as ALI.

We were not able to justifiably compare the correlation of CRP and outcome between young children and adolescents, as only 14 children included in the study were above the age of 10. However, in these 14 children, increased CRP levels seemed also to be associated with adverse outcome (data not shown).

Other differences besides age might explain the contradictive findings between our study and the work of Bajwa et al. Firstly, it is important to realize that corticosteroid treatment and liver failure, both associated with lower CRP levels, did not occur in our cohort. Secondly, patients with septic shock are overrepresented in the Bajwa cohort compared with ours. However, in a study by Claeys et al., CRP levels at time of diagnosis of septic shock in adults did not correlate with favorable outcome [4]. Thirdly, mortality in our cohort was lower, as one would expect when comparing adult and pediatric ICU patients. In both our study and that of Bajwa et al., age is associated with increased mortality. This finding has been reproduced in both adult and pediatric studies, again underscoring the importance of age with regard to ALI/ARDS [3, 5].

A limitation of our study was its retrospective design. To minimize selection bias, decisions on exclusion of patients were made before data on mortality and CRP levels were disclosed. Due to our design, it was not possible to evaluate the association between progression of CRP levels and outcome. In septic shock in adults, decreasing CRP levels 5 days after diagnosis have been associated with improved survival [4]. In addition, the mortality rate was low in our cohort and there was heterogeneity in the actual causes of death, which weakens our comparison between survivors and nonsurvivors. However, in our other endpoint VFDs, we also did not find an association between increased plasma CRP levels and favorable outcome.

In the majority of cases, the ICU treatment was terminated based on the presence of extensive brain damage. This limits the probability that an effect of CRP levels on the extent of inflammation in the lung could potentially be associated with a change in mortality. In a sedation study in mechanically ventilated adults, high CRP levels were associated with longer duration of brain dysfunction but not with death [12]. The brain damage, that explains half of the mortality in our study, might be attributed to hypoxia due to ALI but could also have been caused by, e.g., cardiovascular failure. Taken together, VFD might be a more useful outcome measure than mortality to study such a local pulmonary effect. However, any variable that prolongs the length of mechanical ventilation, such as institutional practices regarding sedation and weaning, may impact VFD, which hampers standardization.

We conclude that increased plasma CRP levels in children with ALI are not associated with favorable outcome in terms of 28-day mortality and VFD. This adds to

Table 2 Uni- and multivariable logistic regression analyses to evaluate the association between plasma C-reactive protein (CRP) level and mortality in pediatric acute lung injury

Variables included in the logistic regression analysis model	Odds ratio for mortality 10 mg^{-1} L difference in CRP level (95 % CI)	Variance in mortality explained by model (Nagelkerke R^2)
CRP	1.087 (1.021–1.158)	0.135
CRP and PRISM	1.108 (1.033–1.188)	0.409
CRP and male gender	1.094 (1.021–1.171)	0.198
CRP and age	1.062 (0.991–1.139)	0.160
CRP and leukocyte count	1.090 (1.023–1.162)	0.144
CRP and tidal volume	1.079 (1.006–1.158)	0.086
CRP and PEEP	1.074 (1.001–1.152)	0.146
CRP and cardiovascular failure	1.047 (0.973–1.126)	0.452

PRISM pediatric risk of mortality, *PEEP* positive end expiratory pressure

existing evidence that ALI in children and adults are not readily comparable and current and future researchers should be cautious to extrapolate data from both epidemiological and pathophysiological studies in adults with ALI to the pediatric population. In clinical practice, CRP levels are not useful to identify children at risk for severe outcomes in ALI.

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Conflict of interest The authors declare that they have no conflict of interest.

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