Original Article

Preoperative C-reactive protein - Albumin ratio as a predictor of requirement for postoperative mechanical ventilation after non-cardiac surgery under general anaesthesia: A prospective observational study (HICARV)

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ABSTRACT

Background and Aims: Mechanical ventilation is an essential but limited resource worldwide. Appropriate perioperative utilisation of such useful resource demands in time prediction where literature does not have enough data. High C-reactive protein (CRP) and low albumin both represent a state of exaggerated inflammation and poor nutrition, the combination of which might represent the sick surgical patients. Therefore, we tried to evaluate the performance of ratio between preoperative CRP and albumin (CAR) for the prediction of postoperative mechanical ventilation. **Methods:** After approval from the ethics committee and trial registration, the study was carried out over 2 years. It included 580 adults undergoing non-cardiac surgeries under general anaesthesia. Blood samples were collected for estimation of CRP and albumin, and all were followed up for the need of mechanical ventilation in the postoperative period till hospital discharge. **Results:** Sixty-six of the analysed 569 patients (11.6%) required postoperative mechanical ventilation in whom the median CAR was higher {0.38 (0.10, 1.45)} than those who did not require the same {0.20 (0.07, 0.65)}, although not statistically significant. A ROC curve analysis found that there is a 58% chance that a CAR will distinguish between the patients requiring postoperative mechanical ventilation from those who do not (AUC = 0.58), which is statistically significant (*P* value = 0.024). Logistic regression did not result in a significant odds of mechanical ventilation with higher ratio {Odds ratio = 1.06 (0.98, 1.16)}. **Conclusions:** High CRP–albumin ratio was found to be associated with higher need for mechanical ventilation in patients undergoing surgery under general anaesthesia, but failed to predict the need for mechanical ventilation.

Key words: C-reactive protein, mechanical ventilation, postoperative period, serum albumin

INTRODUCTION

Mechanical ventilation in Intensive Care Unit (ICU) is an essential, expensive and a limited resource worldwide. Mechanical ventilation in the postoperative period adds to the morbidity and mortality of surgical patients. In addition, it incurs extra stress on the patient, family and economic burden on the hospital.[1] Hence, preoperative prediction of the same contributes to adequate optimisation and effective utilisation of the available resources. Unfortunately, the literature only

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provides us with predictors for mechanical ventilation in a very limited set of patients[2,3] leading to difficulty in the majority of other group of surgical patients.

Peri-operative inflammation is a state of high demand. Low albumin is a sign of poor nutritional status. Additionally, serum albumin being a negative acute phase reactant, the level is usually low in patients with heightened inflammation.[4] C-reactive protein (CRP) being a positive acute phase reactant, its level is usually raised in cases of any inflammation or any infections.[5] CRP–albumin ratio (CAR) has been widely proven as a prognostic indicator and mortality predictor in patients with various malignancies and severe sepsis.[6]

To the current date, we do not have a single simple preoperative predictor for postoperative need of mechanical ventilation. CAR, being a composite but simple parameter found useful in different conditions with high inflammation rate, we evaluated the utility of higher preoperative CAR as a predictor for the requirement of mechanical ventilation postoperatively (HICARV study).

METHODS

This study was carried out in the operation theatre complex of a tertiary care centre with 1000 beds from February 2018 to October 2019. The study was approved by the Institutional Ethics Committee followed by study registration with the Clinical Trials Registry of India (CTRI). The data analysis and statistical plan was written and posted on a publicly accessible server (http://ctri.nic.in) before data were accessed. This manuscript adheres to the applicable Strengthening The Reporting of OBservational studies in Epidemiology (STROBE) guidelines.

This was a prospective observational study conducted in all adult patients undergoing elective and emergency non-cardiac surgeries at a tertiary healthcare institute under general anaesthesia with endotracheal intubation. Patients already on mechanical ventilation before surgery were excluded.

Initially, a detailed participant information sheet was given to all the patients containing information regarding the various elements of the study protocol. This was followed by obtaining written informed consent. In the preoperative area, one venous blood sample of 3 ml was collected from all patients for estimation of CRP and albumin. Thereafter, they underwent the respective surgery under standard general anaesthesia with endotracheal intubation. All patients were followed for the need of mechanical ventilation in the postoperative period till hospital discharge.

A sample size of 569 was required to perform a logistic regression to find a relationship between the CAR and the odds of a patient requiring mechanical ventilation in the postoperative period. The odds ratio was fixed as 2, and the baseline proportion of patients requiring ventilation was taken as 0.04 as collected from our own hospital ICU records. This achieves a power of 90%, and the alpha error allowed was 5%.

The normality of the distribution of data was assessed using Shapiro–Wilk test. To find association with mechanical ventilation, Mann–Whitney U-test was used for CRP–albumin ratio; CRP, albumin, age, body mass index (BMI), fluids, blood loss, duration of surgery and Chi-square test were used for area of surgery, malignancy, American Society of Anaesthesiologists (ASA) grading, Mallampati grading and vasopressor usage, and Fisher exact test was used for the type of surgery.

P value <0.05 was considered to be statistically significant. Univariate and multivariate logistic regression analysis was done to find the association of all and each of the significant factors with the outcome.

RESULTS

A total of 569 subjects were analysed [Figure 1]. The median age of the males in the study was

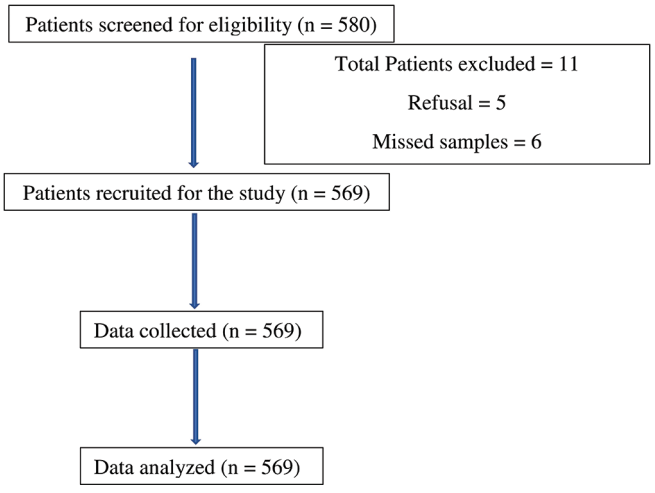

Figure 1: STROBE diagram depicting the flow of patients into the study

45 years (interquartile range/IQR: 33, 58) while that of females was 40 years (IQR: 30, 50). Majority of the study participants fell into less than 40 years (46.2%) age category followed by 40–60 years (40.2%) and 60 years or above age group (13.5%). Gender distribution of the study participants showed a higher proportion of males (53.4%) compared to females (46.6%).

Median body mass index (BMI) of the male subjects was 22.3 kg/m^2 (IQR: 19.1, 24.8) compared to 22.0 kg/m^2 (IQR: 19.5, 25.0) for females. Table 1 depicts the other patient characteristics like region-wise distribution of disease for which surgery was planned, presence of malignancy, American Society of Anaesthesiologists physical status classification (ASA), and difficult airway as detected in the preanaesthetic clinic evaluation, and the nature of surgery.

ICU admission was required for 27.1% of the patients for various reasons. Vasopressors were required in only 17.0% of the patients. Postoperative mechanical ventilation was required in 66 patients (11.6%). Amongst those, 43 were males and 23 were females. Mean duration of the mechanical ventilation was 213.7 ± 1032.4 minutes. Gender, organ involvement, malignancy, difficult airway, vasopressors, intraoperative fluid administration, blood loss, ICU admission and duration of surgery were significantly different in those patients who required mechanical ventilation, whereas parameters like BMI, ASA class, nature of surgery were found to be insignificant [Table 1]. Evaluation of laboratory parameters suggested that median CR*P* value was higher in those patients who required mechanical ventilation but was not statistically significant. We found a statistically significant difference in the median levels of albumin and CAR in mechanical ventilation group as compared to those who did not [Table 2].

Since albumin and CAR were significantly different in patients requiring mechanical ventilation, we applied

Table 1: Patient baseline characteristics and postoperative mechanical ventilation

Variables	No mechanical ventilation *n*-503	Mechanical ventilation *n*-66	*P*
Age in years* [Median (IQR)]	42.0 (31.0, 54.0)	45.0 (35.7, 57.0)	0.08
Gender			
Male	261 (85.9%)	43 (14.1%)	0.04‡
Female	242 (91.3%)	23 (8.7%)	
BMI* in kg/m^2 [Median (IQR)]	22.2 (19.5, 25.0)	22.0 (19.0, 23.9)	0.13
Surgery			
Head and neck	148 (77.1%)	44 (22.9%)	
Thorax	59 (93.7%)	4 (6.3%)	<0.001‡
Abdomen and pelvis	229 (92.7%)	18 (7.3%)	
Others	67 (100.0%)	0 (0%)	
Malignancy			
Absent	346 (92.0%)	30 (8.0%)	<0.001‡
Present	157 (81.3%)	36 (18.7%)	
ASA§ Grade			
I	378 (88.3%)	50 (11.7%)	0.91
II	125 (88.7%)	16 (11.3%)	
Difficult airway (MPG§ ≥3)			
Absent	412 (90.4%)	44 (9.6%)	0.00‡
Present	91 (80.5%)	22 (19.5%)	
Nature of surgery			
Elective	479 (88.9%)	60 (11.1%)	0.14†
Emergent	24 (80.0%)	6 (20.0%)	
ICU admission			
No	415 (100%)	0 (0%)	<0.001
Yes	88 (57.1%)	66 (42.9%)	
Vasopressor requirement			
No	445 (94.1%)	28 (5.9%)	<0.001
Yes	58 (60.4%)	38 (39.6%)	
Intraoperative fluids (ml)*	1200 (1000, 1700)	2500 (2000, 3000)	<0.001
Blood loss (ml)*	150 (70, 250)	500 (350, 800)	<0.001
Duration of surgery (mins)*	150 (110, 200)	352.5 (267.5, 430)	<0.001

*Body mass index (BMI); median with inter-quartile range (IQR) after Mann-Whitney *U*-test. †Fisher exact test was used to calculate *P*, rest all were calculated using Chi-squared test. ‡Refers to P found statistically significant (*P*≤0.05). §ASA – American Society of Anaesthesiologists; MPG – modified Mallampati grading

ROC curve to find out whether both the laboratory parameter discriminate between the requirement of mechanical ventilation or not. Figure 2 shows the ROC curve for albumin and CAR along with the need for mechanical ventilation, respectively. The area under the curve (AUC) for albumin was 0.61 ($P = 0.004$) and 0.58 for CAR (P value = 0.02) which were statistically significant. In the logistic regression analysis, after adjusting all the other variables, duration of surgery remained significantly associated with mechanical ventilation requirement [Table 3].

A subgroup analysis of the CAR and its association with need for mechanical ventilation in patients with different malignancies was done. This revealed no significant association between CAR and need for ventilation even though the ratio was higher in patients requiring postoperative mechanical ventilation [Table 4].

Table 2: Comparison of blood parameters with mechanical ventilation

Variables	No mechanical ventilation		Mechanical ventilation		*P*
	Median	IQR (Q1, Q3)	Median	IQR (Q1, Q3)	
CRP[1] (mg/dl)	0.68	0.21, 2.06	0.96	0.29, 3.86	0.074
Albumin (g/dl)	3.5	2.5, 4.0	3.25	2.15, 3.70	0.004*
CAR[2]	0.20	0.07, 0.65	0.38	0.10, 1.45	0.024*

*Refers to P found statistically significant ($P \leq 0.05$). CRP – C-reactive protein, CAR – CRP–albumin ratio

DISCUSSION

We observed CAR was significantly higher in patients requiring mechanical ventilation postoperatively as

Table 3: Logistic regression analysis

Variables	Odds ratio	95% confidence interval		*P*
		Lower limit	Upper limit	
Age	1.00	0.97	1.04	0.75
Male Gender	0.80	0.32	2.05	0.65
BMI[1] (Kg/m^2)	0.97	0.87	1.09	0.63
Malignancy (reference non-malignancy)	1.24	0.46	3.32	0.08
Difficult airway (absent as reference)	1.22	0.32	2.23	0.74
Type of surgery (elective)	2.92	0.44	19.51	0.27
IV fluid	1.00	0.99	1.00	0.86
Blood loss	1.00	1.00	1.00	0.18
Vasopressor (absent as reference)	1.51	0.60	3.77	0.38
Duration of surgery	1.01	1.00	1.01	0.001*
CRP[2] (mg/L)	0.98	0.92	1.03	0.41
Albumin (g/dl)	0.73	0.43	1.25	0.25
CAR[3]	1.06	0.98	1.16	0.16

*Refers to *P* found statistically significant ($P \leq 0.05$). BMI – Body mass index, CRP – C-reactive protein, CAR – CRP–albumin ratio

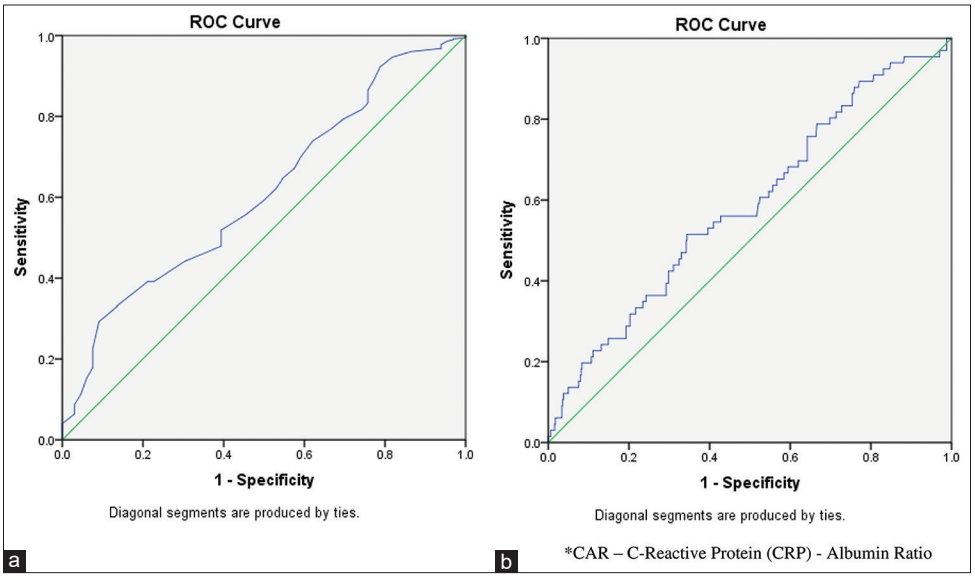

Figure 2: Receiver operating characteristics curve for albumin levels and CRP-albumin ratio with mechanical ventilation requirement after surgery. (a) For albumin levels, (b) For CRP-albumin ratio

Table 4: Association of CAR[1] with the need for mechanical ventilation amongst patients with malignancy

	n (%)	CAR [Median (IQR)]	*P*
No mechanical ventilation	157 (81.3)	0.22 (0.09, 0.62)	0.09
Mechanical ventilation	36 (18.6)	0.40 (0.11, 0.99)	

CAR – CRP-albumin ratio

compared to those who did not require it, but it did not predict the same.

The CAR has been used in critically ill and malignant populations to assess varying outcomes. It has been found to be a predictor of long-term morbidity and mortality in critically ill[7-9] and a predictor of overall survival, cancer-free survival, recurrence-free survival in malignant patients.[6,10-14] To our knowledge, this ratio has never been studied as a marker to predict postoperative mechanical ventilation.

Surgical patients with different diseases have a combination of high CRP and low albumin resulting in a high CAR. CRP is a positive acute phase reactant; hence, its levels often increase secondary to inflammation, whereas serum albumin drops as it is a negative acute phase reactant.[15] In addition, undernutrition is often an accompaniment of different disease states further aggravating hypoalbuminaemia.[16] Therefore, the chances of such patients requiring mechanical ventilation support after surgery are expected to be higher.

A higher ratio with insignificant odds for predicting need of mechanical ventilation probably is a reflection of heterogenous groups of study participants. Additionally, the CRP value in itself varies during different time course of any disease in a given patient, who may present to the hospital during varying time periods of their disease course.[17] This would have affected the estimation of CRP and hence the ratio. Further, need for mechanical ventilation for a patient depends upon multiple factors like blood loss, blood transfusion and crystalloid transfusion.[18]

To the best of our knowledge, most of the published studies evaluating CAR and outcomes are retrospective in nature.[8,14,19,20] In contrast, the present study has the strength of a prospectively planned study and to follow outcome till the end.

CAR was found to be the predictor of overall survival and cancer-free survival in patients with malignancy.[6,10-14] Jabs *et al*.[21] demonstrated an enhanced expression of CRP by the cancer cells in renal cell carcinoma (RCC). Similarly, Sim *et al*.[22] and Steffens *et al*.[23] found an elevated CRP was associated with poorer survival in RCC patients. Szkandera, *et al*.[24] reviewed 304 patients and found that elevated CRP level is associated with poor survival in patients with soft tissue sarcoma. This conclusion was also corroborated by a meta-analysis done by Li *et al*.[25] In contrast, we found that the CAR did not predict the need of postoperative mechanical ventilation in the subset of our malignant patients. The reasons for such findings might be indicative of different behaviour of malignancy at different stages of the disease. Additionally, the primary outcome parameter in question probably matters. Although both mechanical ventilation and survival are valid outcome parameters with their own importance, the former one is a short-term outcome, whereas the latter is a long-term outcome. Hence, CAR may predict survival but not ventilation.

Preoperative hypoalbuminaemia is associated with higher mortality in patients who underwent surgery for RCC.[26] Liang *et al*.[27] found significant relationship amongst CRP, albumin and survival in soft tissue sarcoma patients. We found serum albumin was significantly lower in patients who required postoperative mechanical ventilation.

Guo *et al*. found low CAR to be associated with the early stages of RCC, whereas high CAR presents in the advanced or metastatic RCC suggesting that CAR could be a new prognostic indicator related to its progression.[11] More importantly, they also found that CAR is a predictor for recurrence of localised RCC who underwent full resection. Similarly, Shibutani *et al*.[28] concluded CAR to be a useful prognostic marker in patients with colorectal cancer who undergoing curative surgery. Other researchers found that increased CAR was significantly associated with larger tumour size, higher tumour grade and more advanced stages in soft tissue sarcoma patients,[27] pancreatic duct all cancer,[29] and laryngeal cancer.[30] Although not statistically significant, we observed a higher CAR in patients who required postoperative mechanical ventilation than in those who did not.

A few limitations of our study are inclusion of heterogeneous surgical patients and trying to predict an outcome with a single preoperative CAR. In spite of these, our study findings suggest higher CAR defines a possible need for postoperative mechanical ventilation. But this value alone cannot be used as a

predictor for the same. CAR should be used only as a tool in conjunction with the clinical judgement till some future studies are exploring it further especially in different sub-groups like malignancy, ASA III or more, and those undergoing different categories of surgeries.

CONCLUSION

In summary, the CAR was found to be a valuable predictor of outcome in both critically ill and cancer patients similar to our findings. Although the results were statistically insignificant, an observation of higher CAR associated with higher need for mechanical ventilation is getting reflected sans prediction. Additionally, preoperative CAR will help us to triage the need of postoperative mechanical ventilation. To conclude, our study results indicate a higher preoperative CAR is associated with a need for postoperative mechanical ventilation in patients undergoing surgery under general endotracheal anaesthesia. This shall add to the optimisation of available limited resources.

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Conflicts of interest

There are no conflicts of interest.

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