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ORIGINAL SCIENTIFIC REPORT

Advanced Modeling to Predict Pneumonia in Combat Trauma Patients

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Abstract

Background Tools to assist clinicians in predicting pneumonia could lead to a significant decline in morbidity. Therefore, we sought to develop a model in combat trauma patients for identifying those at highest risk of pneumonia.

Methods This was a retrospective study of 73 primarily blast-injured casualties with combat extremity wounds. Binary classification models for pneumonia prediction were developed with measurements of injury severity from the Abbreviated Injury Scale (AIS), transfusion blood products received before arrival at Walter Reed National Military Medical Center (WRNMMC), and serum protein levels. Predictive models were generated with leave-one-out-cross-validation using the variable selection method of backward elimination (BE) and the machine learning algorithms of random forests (RF) and logistic regression (LR). BE was attempted with two predictor sets: (1) all variables and (2) serum proteins alone.

Results Incidence of pneumonia was 12% (n = 9). Different variable sets were produced by BE when considering all variables and just serum proteins alone. BE selected the variables ISS, AIS chest, and cryoprecipitate within the first 24 h following injury for the first predictor set 1 and FGF-basic, IL-2R, and IL-6 for predictor set 2. Using both variable sets, a RF was generated with AUCs of 0.95 and 0.87—both higher than LR algorithms.

Conclusion Advanced modeling allowed for the identification of clinical and biomarker data predictive of pneumonia in a cohort of predominantly blast-injured combat trauma patients. The generalizability of the models developed here will require an external validation dataset.

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Background

Nosocomial infections are frequent complications of the critically ill trauma patient. With a reported incidence as high as 50%, they are the leading cause of late death following traumatic injury [1–3]. Pneumonia is the most common nosocomial infections in the intensive care unit population and a significant complication among trauma patients [4–6]. The majority of nosocomial pneumonias that develop in the critically ill are ventilator-associated pneumonias (VAP), and among trauma patients, the prevalence of VAP has been reported to be four times higher than that in non-trauma patients [7–9]. The downstream consequences of a patient developing a nosocomial pneumonia are substantial. It is associated with an increase in the number of days of mechanical ventilation, intensive care unit (ICU) length of stay, and overall hospital length of stay [10, 11]. In addition, pneumonia is the leading cause of death among nosocomial infections with corresponding mortality rates of 20% in trauma patients and as high as 80% in patients with VAP [5, 12]. Furthermore, the burden to the healthcare system has been estimated to cost billions of dollars [13, 14].

Recognizing the clinical and economic implications of nosocomial pneumonia has led to the implementation of widespread strategies to prevent its occurrence [15, 16]. Despite these initiatives, the risk of pneumonia remains a critical problem. While several independent risk factors have been associated with nosocomial pneumonia, current diagnostic tools include variables from symptomatic patients [17, 18]. Thus, the use of these algorithms, unfortunately, leads to late diagnosis and treatment often after the patient has clinically deteriorated. The ability to predict who will develop pneumonia prior to the onset of symptomatic declines could prove to be highly beneficial. A clinical decision support (CDST) designed to assist clinicians in predicting those patients at highest risk of nosocomial pneumonia could lead to improved preventative strategies and earlier diagnosis.

In that regard, we sought to develop a predictive model to identify patients at higher risk of nosocomial pneumonia in a cohort of combat trauma patients as a stepping stone to creating a CDST. We hypothesized that we could accurately predict those injured service members at highest risk of nosocomial pneumonia through advanced modeling.

Methods

This retrospective study of combat casualties with extremity wounds injured in Iraq or Afghanistan and evacuated to a single continental US military treatment facility between 2007 and 2012 was approved by the Walter Reed National Military Medical Center (WRNMMC) Institutional Review Board (IRB). This work was done under the umbrella of the Surgical Critical Care Initiative (SC2i), a multi-institutional military–civilian collaboration and a center at the Uniformed Services University of Health Sciences. These prospective data informed the development of a CDST for timing of wound closure. As part of an ongoing analysis, we looked at other outcomes including pneumonia.

Modeling was performed with the statistical programming language of R (version 3.3.3) upon the operating system macOS Sierra 10.12.6. Random forest models were generated with the *ranger* package (version 0.10.1), which has a C++ back-end [19]. Logistic regression is a function provided by base R. The backward elimination procedure described below was generated in-house. ROC curves were generated with the *pROC* package (version 1.13.0) [20]. Boxplots were generated with the *ggplot2* package (version 2.2.0).

Pneumonia incidence

All cases of nosocomial pneumonia were defined with radiographic imaging (chest X-ray or computed tomography) concerning for pneumonia (infiltrate, consolidation, or cavitation), isolated organism on quantitative respiratory culture (10^5 organisms by bronchial alveolar lavage or 10^6 organisms on tracheobronchial aspirate), and treatment with a course of antibiotics. Ventilator-associated pneumonia was defined as the above in the setting of casualties mechanically ventilated for greater than 48 h.

Variable collection

Potential predictors—a total of 44 variables—included measures of injury severity, transfusion blood products received, and serum protein levels. The potential variables were present for each member of our cohort, and this allowed us to use it in entirety (see Table 1 for full list). The injury severity measures were the multiple body region-specific values for Abbreviated Injury Scale (AIS) and the single-composite Injury Severity Score (ISS). The transfusion blood product variables consisted of red blood cells, whole blood cells, platelets, fresh frozen plasma, and cryoprecipitate—separate measures were used for those delivered on the field (within 24 h of injury) or during hospitalization at WRNMMC. Serum samples were assayed for a panel of 32 inflammatory cytokines using the Luminex platform. Serum collection and biomarker analysis have been previously described [21]. Briefly, peripheral blood was collected prior to each surgical debridement occurring in the continental USA. Serum was subsequently fractionated and stored at − 70C until analysis. Serum was

then analyzed using both Beadlyte® Human 30 and 2-plex cytokine detection systems on the Luminex® 100 IS xMAP Bead Array Platform (Millipore Corp., Ontario, Canada). Reported serum measurement is based on either one or two measurements. Values lower than the lower limit of detection were set to the threshold value, and less frequently, a similar adjustment was made for being above the upper limit.

Variable selection

The 44 potential predictive variables were reduced with backward elimination (BE) to two smaller subsets via complementary approaches: (1) initiated with all variables (clinical and serum proteins) and (2) using only serum proteins after removing highly correlated ones ($r > 0.3$). A random forest (RF) was used for the BE process. The "backward" nature of the process lends itself to variables being eliminated if they provide redundant information. BE was employed with the initial feature set by first determining the number of iterations required for a baseline level of RF overall performance (OP) with a derived metric consisting of the sum of AUC and sensitivity/specificity (defined at the threshold where their product is maximized). A "baseline level" was determined by requiring OP to remain "similar" for 4 increases in the number of iterations with steps sizes of 50. "Similar" was defined as OP not changing by more than 0.01. Following the determination of the number of iterations, the effect of dropping variables was assessed by dropping variables one-at-a-time. A variable was dropped if OP decreased by more than 0.02. BE was run recursively till the features in the model remained constant. After the selection of the final set of features, if needed, additional iterations were run for convergence—defined as a combined change of < 0.01—of AUC, sensitivity, and specificity.

Employed machine learning algorithms

The machine learning methods used here consisted of the random forest (RF) with BE and also logistic regression (LR). LR was used with the variables resulting from BE. The following RF tuning parameters were employed: minimum bucket size = 5, mtry = square root of the number of features, and number of trees = 500. Multiple iterations of leave-one-out-cross-validation (LOOCV) were used for the generation of LR and RF models. For each iteration, a pair of patients (1 control, 1 case) was held out of for testing, and the remaining patients were upsampled to create a balanced cohort for training. Test patient probabilities were aggregated across iterations to generate ROC curves.

Results

A total of 73 patients were enrolled during the study time period. All casualties in our cohort were males (age in years: median = 22, first quartile = 20, third quartile = 30). The primary mechanism of injury was blast (91%), and the average injury severity score (ISS) was strongly skewed (median = 16, first quartile = 10, third quartile = 22). Almost half (44%) of the patients sustained a major vascular injury, and there were 116 extremity wounds among the 73 casualties; our cohort included those with single extremity wounds as well as those with multiple injuries. Patients underwent a median of three operations after arrival to WRNMMC. The incidence of pneumonia in our cohort was 12% (9/73). Of the nine cases of pneumonia, five qualified as VAP ($\sim$ 56%). As in other studies, the occurrence of pneumonia was associated with overall hospital length of stay, number of days on a ventilator, and the number of ICU days (Wilcoxon rank-sum tests, p values $<< 0.01$).

Before attempting to build a binary classification model for the prediction of pneumonia, we determined whether potential variables (blood products received, injury severity measures, and serum protein) were collected prior to the date of pneumonia diagnosis. Both blood products and injury severity variables were collected prior to diagnosis. However, serum was collected prior to diagnosis for seven of nine patients with pneumonia ($\sim$78%); pre-diagnosis serum collection days were 1, 2, 9, 10, 16, 32, and 41. However, serum was collected prior to diagnosis for seven of nine patients with pneumonia ($\sim$78%); pre-diagnosis serum collection days were 1, 2, 9, 10, 16, 32, and 41. For the other two pneumonia patients, serum was collected on the day of diagnosis and 3 days later.

Four models were generated using the two algorithms of RF and LR. Selected variables for the algorithms first were identified by BE performed on all included variables in the dataset and then by BE performed only on serum proteins. Model performance of each algorithm is shown in Table 2. In general, RF outperformed LR regardless of variable set selected. The best model for predicting pneumonia was the RF algorithm using the variables ISS, AIS chest, and cryoprecipitate given within the first 24 h, which were selected from BE performed on all included variables in the

Table 1 Potential variables

Clinical variables	Serum variables
AIS (head)	Epidermal growth factor
AIS (face)	Eotaxin
AIS (chest)	Basic fibroblast growth factor
AIS (abdomen)	Granulocyte colony-stimulating factor
AIS (extremity)	Granulocyte–macrophage colony-stimulating factor
ISS	Human hepatocyte growth factor
Red blood cells	Interferon alpha
Whole blood	Interferon gamma
Platelets	Interleukin-1 alpha
Fresh frozen plasma	Interleukin-1 beta
Cryoprecipitate	Interleukin-1 receptor antagonist
	Interleukin-2
	Interleukin-2 receptor
	Interleukin-3
	Interleukin-4
	Interleukin-5
	Interleukin-6
	Interleukin-7
	Interleukin-8
	Interleukin-10
	Interleukin-12
	Interleukin-13
	Interleukin-15
	Interleukin-17
	Interferon gamma-inducible protein
	Monocyte chemoattractant protein-1
	Monokine induced by interferon-gamma
	Macrophage inflammatory protein-1 alpha
	Macrophage inflammatory protein-1 beta
	RANTES
	Tumor necrosis factor alpha
	Vascular endothelial growth factor

dataset. This RF algorithm produced a sensitivity of 1.0, specificity of 0.89, and AUC of 0.97. ROC curves for the four algorithms are shown in Fig. 1. The solitary contributions of each variable can be seen from the plots (Fig. 3) in Figs. 2 and 3.

Discussion

We developed several predictive models for the development of pneumonia in our cohort of combat casualties. Our models are meant to serve the purpose of risk stratification which will be used to determine specific treatments. Given that our dataset consisted of a military trauma cohort, we modeled with and without clinical and demographic variables—our reasoning being that a model with serum proteins alone may be more generalizable to a civilian population. It is likely that a civilian cohort may differ from our military cohort in terms of injury severity as reflected by variables such as ISS and the amount of transfused cryoprecipitate—variables selected in our modeling process. However, a civilian cohort may express similar serum protein expression to combat casualties, which could reflect more on the inflammatory processes leading to pneumonia, regardless of the injury severity. Moving forward, we plan to externally validate beyond combat casualties and refine these models with civilian trauma and non-trauma critically ill patients.

The machine learning algorithms of random forest (RF) and logistic regression (LR) were chosen because of their complementary strengths. The RF algorithm has consistently demonstrated strong classification performance [22]. A relative strength of the RF algorithm is its ability to handle many predictive variables relative to the number of observations (i.e., patients). In contrast, the LR algorithm's benefits include the ease of interpretability and its common utilization in clinical research.

Predictive modeling and the use of CDSTs are not a novel concept. The Laboratory Risk Indicator for Necrotizing Fasciitis (LRINEC) score, the Alvarado score for appendicitis, and the Clinical Pulmonary Infection Score (CPIS) are all examples of previously developed and currently operational tools [18, 23, 24]. The CPIS tool has been shown to have moderate reliability and accuracy in diagnosing nosocomial pneumonia [25, 26]. However, much like other tools, CPIS is based on radiographic and laboratory values after the patient has become symptomatic. Thus, CPIS may assist with narrowing clinician's differential for a patient's decompensation, but treatment becomes delayed instead of proactive.

Several previous studies have identified predictive risk factors for nosocomial pneumonia in trauma patients. Antonelli and colleagues found that combined thoracic and abdominal injury increased the risk of early onset pneumonia 11-fold in trauma patients [17]. In addition to thoracic trauma, others have found traumatic brain injury, age, and ventilator days as independent predictors for the development pneumonia among traumatically injured patients [27, 28]. In patients with retained hemothorax, blunt mechanism of injury and failure to administer preprocedural antibiotics prior to tube thoracostomy were found to be independent predictors for pneumonia [29]. Similar to these previous studies, we identified chest injury as a risk factor. However, with supplementary cytokine analysis we were able to identify additional factors to predict the development of pneumonia in our cohort: FGF-basic (FGF2), IL-2R (soluble), and IL-6. FGF-basic has been shown to be involved in a variety of functions including angiogenesis [30]. Soluble IL-2R has been found to be elevated in blunt trauma and thermal injury patients, and it has been demonstrated to induce alterations in T-cell mediated immune function [31]. IL-6 is promptly produced in response to tissue injury and has been shown to be correlated with severity of injury and complications such as infections [32]. In particular, IL-6 was recently identified as a potential marker for pneumonia in brain injured patients [33].

The ability to accurately predict which patients will develop pneumonia could provide the opportunity to change clinical practice and reduce the incidence of pneumonia. It is anticipated that a predictive tool could lead to the implementation of more aggressive prophylactic measures or the initiation of antibiotics earlier in the patient's hospital course. It could be argued that initiating antibiotics in this instance could be considered prophylactic, which have not been shown to be beneficial [34]. However, starting antibiotics should be considered therapeutic in the setting of an earlier diagnosis as opposed to treatment based on symptoms and clinical deterioration. In essence, a CDST could adapt and tailor management by providing individualized and patient-focused care.

Diagnosing nosocomial pneumonia in a critically ill trauma patient can be challenging. Processing clinical, radiographic, and laboratory information often is not straightforward particularly in a complex patient. Diagnosis and subsequent treatment then can be delayed which can lead to increased morbidity and mortality for the patient. It has been reported that errors such as these delays in diagnosing pneumonia result in almost 100,000 deaths a year [35]. Likewise, the development of pneumonia and other nosocomial infections results in a substantial financial burden to the healthcare system. It is estimated that the prevention of pneumonia could lead to $1.9 billion and $10.1 million in annual cost-savings for the US healthcare system and the US Military Health System, respectively [36]. Without a commitment to improving diagnoses and

Table 2 Model features and performance

	Selected variables	Model	AUC	Sensitivity	Specificity
Backward elimination with all variables	ISS, AIS chest, and cryoprecipitate (received prior to WRNMMC)	RF	0.97	1.0	0.89
Backward elimination with all variables	ISS, AIS chest, and cryoprecipitate (received prior to WRNMMC)	LR	0.86	0.89	0.87
Backward elimination with serum proteins	FGF-basic, IL-2R, and IL-6	RF	0.87	0.78	0.97
Backward elimination with serum proteins	FGF-basic, IL-2R, and IL-6	LR	0.75	0.73	0.76

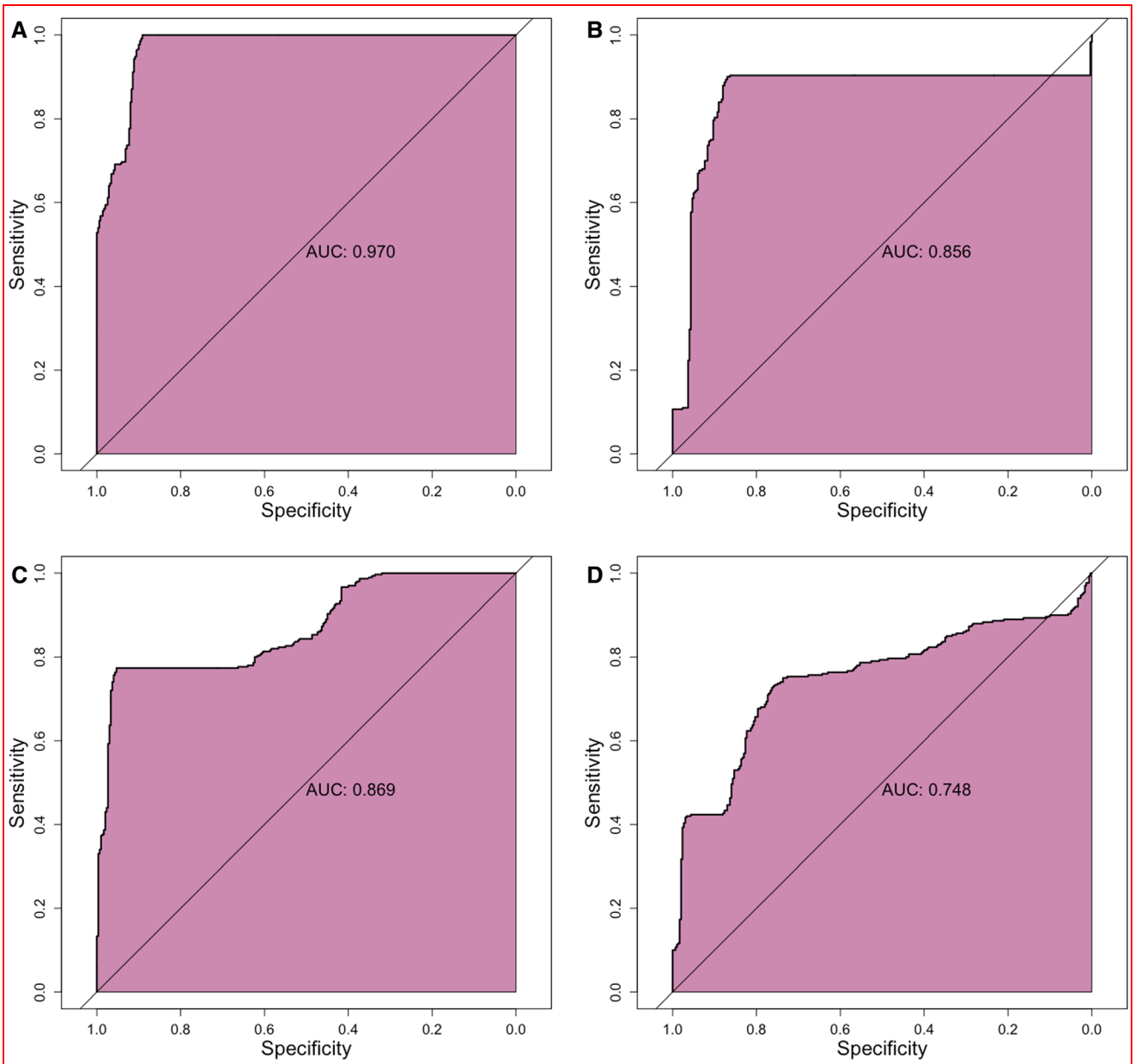

Fig. 1 ROC curves. **a** RF with variables ISS, AIS chest, and cryoprecipitate (received prior to WRNMMC). **b** LR with same variables as in **a**. **c** RF with variables, FGF-basic, IL-2R, and IL-6. **d** LR with same variables as **c**

reducing medical errors, patient safety and outcomes will continue to decline while costs will continue to rise. The impact of predictive modeling and CDSTs on lowering the incidence and/or facilitating earlier diagnosis of certain diseases such as nosocomial pneumonias could prove to be invaluable. Moreover, the Committee on Diagnostic Error in Health Care "concluded that improving the diagnostic process is not only possible, but also represents a moral, professional, and public health imperative" [37].

There are a few limitations of our study that deserve mentioning. Our data were collected from a small and specific cohort of healthy males (18–42 years) sustaining combat-related (blast) extremity injuries. In addition, they were all severely injured and were uniformly treated by specific protocols. Furthermore, there were limited data available prior to arriving to our facility and serum biomarker data were not collected until several days after injury. Finally, casualties underwent transcontinental evacuation and were cared for at multiple military facilities prior to arrival to our institution. Thus, our cohort may not be representative of a more general population and this implies that our models need to be externally validated to

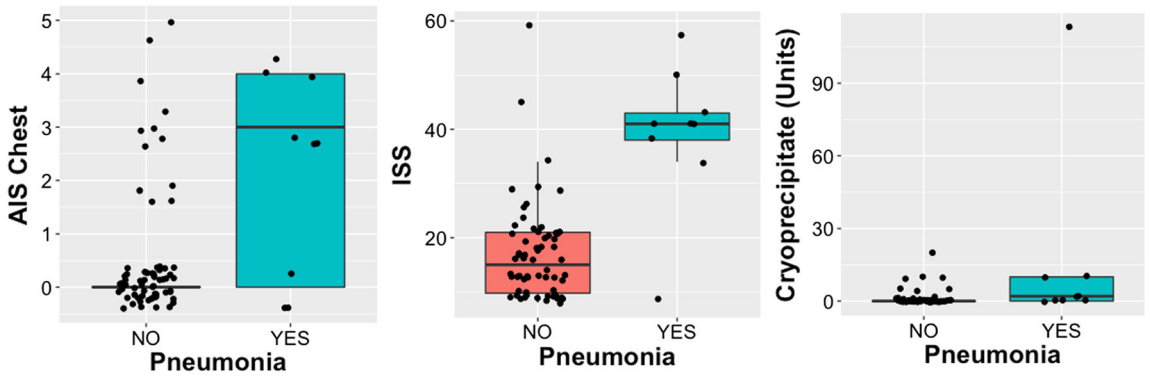

Fig. 2 Relationship between injury-related variables and the incidence of pneumonia. Boxplots are shown for variables selected with BE using all variables. The first and third quartiles are represented by the lower and upper sides of the box. The median is the horizontal line within each box. The individual points represent the raw data

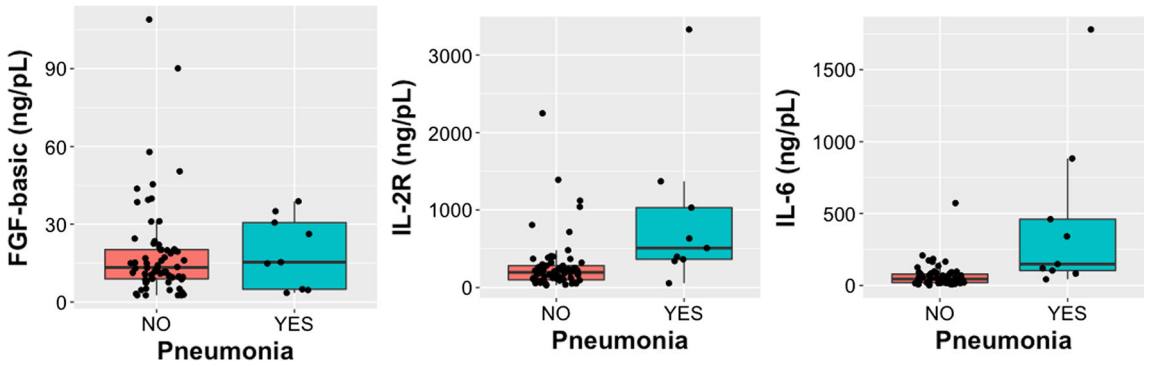

Fig. 3 Relationship between selected serum proteins and the incidence of pneumonia

ensure generalizability. Importantly, we are continuing to collect data on bacterial subgroups and that information may be critical for additional model refinement.

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