Online supplementary material

RISK FACTOR FOR NON-INVASIVE VENTILATION FAILURE IN CRITICALLY ILL PATIENTS WITH CONFIRMED INFLUENZA INFECTION: A CHAID DECISION-TREE ANALYSIS.

Study definitions

*ARF was defined as recent dyspnea with respiratory rate > 25 breaths/minute and/or sternocleidomastoid muscle activation with or without pulmonary infiltrates on chest X-ray (CXR) and hypoxemia (defined as arterial oxygen saturation < 90% by pulse oximetry breathing air) caused by influenza viral infection. Due to the epidemiological nature of the database we do not record the arterial blood gas, PaO2/FiO2 ratio or NIV setting.

*NIV failure was defined as the need for ETI. All patients with NIV failure were subsequently intubated. No patients with NIV failure died before being intubated. Criteria for ETI were at the discretion of the attending physician and according to local standard operating procedures. Causes of NIV failure were not recorded.

*Primary viral pneumonia (PVP) was defined as patients presenting with acute respiratory distress, unequivocal alveolar opacities involving two or more lobes, and negative respiratory and blood bacterial cultures during the acute phase of influenza virus infection (1-6)

*Organ failure was assessed using the Sequential Organ Failure Assessment (SOFA) scoring system (7).

*Community-acquired respiratory co-infection (CARC) was defined as a bacterial respiratory microbiologically-confirmed infection diagnosed within the first two days of hospitalization. For CARC diagnosis, acute pulmonary infiltrate evident on CXR and consistent with pneumonia and confirmatory findings upon clinical examination were required (4). Infections occurring later were considered nosocomial. Hospital-acquired pneumonia was defined based on the current guidelines (8) and excluded for this study.

*Chronic obstructive pulmonary disease (COPD) was determined by premorbid pulmonary function testing, when available. In the absence of documented airflow obstruction, we used clinical criteria, clinical history with compatible physical findings, and/or evidence of hyperinflation on chest radiography, interpreted by the attending pulmonary physicians (9).

According to the observational design of the study a spirometric classification of severity and stages of COPD was not possible.

*Virus-induced COPD exacerbation was defined as a worsening of respiratory symptoms due to proven influenza infection. Patients with diagnosis of COPD exacerbation without confirmed influenza infection was not included.

*Chronic cardiovascular disease was defined as class III and IV of the New York Heart Association Functional Classification (10).

*Obese patients were defined as having a body mass index (BMI) greater than 30 kg/m^2 (11). Acute kidney injury (AKI) definition and staging were established according to the current Acute Kidney Injury Network Classification (12).

CHAID decision-tree algorithm (13-18)

In the first step of the CHAID procedure, the total group of subjects is divided into a number of subgroups on the basis of the variable most strongly associated with the dependent variable (NIV failure). This variable is not predefined by the investigator.

In the second step, the subgroups are split again on the basis of the variable that is then most strongly associated with dependent variable. The procedure is repeated until no variables remain that have a significant association with dependent variable in the subgroups, or until the groups have reached a minimum size previously defined by the investigator according to sample size .

The CHAID algorithm operates using a series of merging, splitting, and stopping steps based on user-specific criteria as follows. The merging step operates using each predictor variable where CHAID merges non-significant categories using the following algorithm (15)

1) Perform cross-tabulation of the predictor variable with the binary target variable.
2) If the predictor variable has only two categories, go to step six.
3) X^2-test for independence is performed for each pair of categories of the predictor variable in relation to the binary target variable using X^2 distribution (df=1) with significance set at 0·05. For non-significant outcomes, those paired categories are merged.
4) For non-significant tests identified by p>0·05, those paired categories are merged into a single category. For tests reaching significance identified by p≤0·05, the pairs are not merged.

5) If any category has less than the user-specified minimum segment size, that pair is merged with the most similar other category.
6) The adjusted p-value for the merged categories using a Bonferroni adjustment is utilised to control for Type I error rate.

The splitting step occurs following the determination of all the possible merges for each predictor variable. This step selects which predictor is to be used to "best" split the node using the following algorithm:

1) X^2-test for independence using an adjusted p-value for each predictor.
2) The predictor with the smaller adjusted p-value is split if the p-value less than the user-specified significant split level are set at 0.05; otherwise the node is not split and is then considered a terminal node.

The stopping step utilises the following user-specified stopping rules to check whether or not the tree growing process should stop.

1) If the current tree reached the maximum tree depth level, the tree process stops.
2) If the size of a node is less than the user-specified minimum node size, the node will not split.
3) If the split of a node results in a child node whose node size is less than the user-specified minimum child node size value, the node will not be split. The parent node is the level where the data set divides into child nodes that can themselves become either parent nodes or end in a terminal or decision node.
4) The CHAID algorithm will continue until all the stopping rules are met.

In our model, we imposed a minimum of 100 patients per node, a significance of p value < 0.05 and a maximum of four levels of partition. We also reviewed the possibility of inconsistent clinical outcomes.

References

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with parental and/or child developmental problems at the start of family support. *BMC Psychiatry*. 2016;16(1):15.

e-Table 1: Gain and index charts for nodes in the classification tree (node by node)

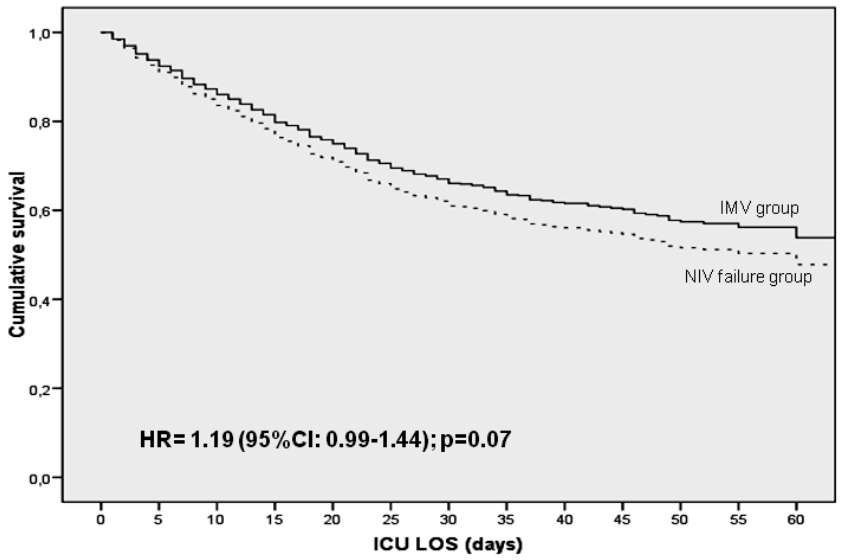
Gain and index charts for nodes

Node	Node		Gain		Response	Index
	N*	Percent +	N	Percent		
4	95	11,8%	70	20,1%	73,7%	170,7%
8	76	9,4%	55	15,8%	72,4%	167,6%
9	69	8,6%	38	10,9%	55,1%	127,6%
5	99	12,3%	50	14,4%	50,5%	117,0%
10	105	13,0%	43	12,4%	41,0%	94,8%
6	128	15,9%	42	12,1%	32,8%	76,0%
7	234	29,0%	50	14,4%	21,4%	49,5%

e-Table 2: Predictive accuracy of the model according to line of branching from exhaustive CHAID tree analysis. (SOFA: Sequential Organ Failure Assessment; COPD: Chronic Obstructive Pulmonary Disease; PPV: Predictive Positive value; PNV: Predictive Negative Value; LH(+) Likelihood ratio positive; LH(-): Likelihood ratio negative)

Line of branching	Sensitivity (%)	Specificity (%)	Pre-Test probability (%)	PPV (%)	PNV (%)	Pre-Test Odds	LH(+)	LH(-)	Post-Test Odds	Post-Test probability (%)
SOFA score ≥ 5	69	60	57	70	59	1.34	1.72	0.52	2.29	70
SOFA score ≥ 5 and > 2 infiltrates in chest x-ray	79	33	65	68	46	1.83	1.17	0.65	2.14	68
SOFA <5 and COPD	46	72	72	82	34	2.63	1.73	0.74	4.56	82
SOFA <5 and non-COPD and >2 infiltrates in chest x-ray	59	55	60	67	47	1.52	1.31	0.74	2.0	67

e-Figure 1:


1,0
0,8
0,6
0,4
0,2
0,0
Cumulative survival
IMV group
NIV failure group
HR= 1.19 (95%CI: 0.99-1.44); p=0.07
0
5
10
15
20
25
30
35
40
45
50
55
60
ICU LOS (days)