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Critical Care 2011, **15**:R66 doi:10.1186/cc10046

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ISSN 1364-8535

Article type Research

Submission date 21 October 2010

Acceptance date 22 February 2011

Publication date 22 February 2011

Article URL <http://ccforum.com/content/15/1/R66>

This peer-reviewed article was published immediately upon acceptance. It can be downloaded, printed and distributed freely for any purposes (see copyright notice below).

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Acute kidney injury in critical ill patients affected by influenza A (H1N1) v infection

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Abstract

Introduction: Little information exists about the impact of acute kidney injury (AKI) in critically ill patient affected by pandemic 2009 influenza A (H1N1) v infection.

Methods: This was a prospective, observational, multi-center study conducted in 148 Spanish intensive care units (ICU). Patients with chronic renal failure were excluded. AKI was defined according to AKIN criteria.

Results: A total of 661 patients were analyzed. One hundred and eighteen (17.7%) patients developed AKI; 37 (31.4%) of the patients with AKI were classified as AKI I, 15 (12.7%) as AKI II and finally 66 (55.9%) as AKI III, of which 50 (75.7%) required continuous renal replacement therapy (CRRT). Patients with AKI had a higher Acute Physiology and Chronic Health Evaluation II (APACHE II) score (19.2 ± 8.3 versus 12.6 ± 5.9 , $P < 0.001$), Sequential Organ Failure Assessment (SOFA) score (8.7 ± 4.2 versus 4.8 ± 2.9 $P < 0.001$), more need of mechanical ventilation (MV) (87.3% versus 56.2% $P < 0.01$ OR 5.3 CI 3.0-9.4), shock (75.4% versus 38.3% $P < 0.01$ OR 4.9 CI 3.1-7.7), multi-organ dysfunction syndrome (MODS) (92.4% versus 54.7% $P < 0.01$ OR 10.0 CI 4.9-20.21) and co-infection (23.7% versus 14.4% $P < 0.01$ OR 1.8 CI 1.1-3.0). In survivors, patients with AKI remained longer on MV, ICU and hospital (length of stay) LOS were longer than patients without AKI. The overall mortality was 18.8% and was significantly higher for AKI patients (44.1% versus 13.3% $P < 0.01$ OR 5.1 CI 3.3-7.9). A logistic regression analysis was performed with AKIN categories and demonstrated that among patients with AKI only AKIN3 was independently associated with higher ICU mortality (OR=4.81; 95% CI 2.17 – 10.62; $P < 0.001$)

Conclusions: In our cohort of patients with pandemic 2009 influenza A (H1N1) v infection only AKI III was independently associated with mortality.

Introduction

Pandemic 2009 Influenza A (H1N1) v Infection was first described in Mexico in April 2009 and several reports have been published regarding the presentation of this disease with severe acute respiratory symptoms in hospitalized patients [1]. However the information regarding the incidence and impact of renal failure among this patients remains scarce. WHO warned physicians that patients affected by Pandemic 2009 Influenza A (H1N1) Virus Infection might develop renal impairment from just mild disease to the need of renal replacement therapy (RRT) [1, 2, 3, 4, 5].

In critical care settings, many studies are limited as they lack a uniform definition of Acute Kidney Injury (AKI). The definitions of AKI varied widely and were predominately based on large increments of serum creatinine, thus ignoring milder stages of AKI. In addition, the choice of using the AKIN criteria was based on the lack of reliance on baseline creatinine on ICU admission. A definition and classification of AKI was established by a consensus of critical care and nephrology societies worldwide [6]. The degree of AKI classified by AKIN criteria correlates with mortality in a progressive fashion, emphasizing the importance of the severity of AKI. This first globally developed AKI definition and classification incorporates the important finding that small increases of serum creatinine in AKI already negatively impact outcome.

The present study aims to evaluate whether the presence of AKI in a cohort of patients hospitalized with a severe presentation of Pandemic 2009 Influenza A (H1N1) Virus Infection in Intensive Care Unit (ICU) was associated with worse outcomes.

Materials and methods

Study data were obtained from a voluntary registry created by the Spanish Society of Intensive Care Medicine (SEMICYUC) after the first reported ICU case (see Additional file 1 for SEMICYUC working group investigators). Inclusion criteria were: fever ($> 38^{\circ}\text{C}$); respiratory symptoms consistent with cough, sore throat, myalgia or influenza-like illness; acute respiratory failure requiring ICU admission; plus microbiologic confirmation of novel influenza A (H1N1) v. Data were reported by the attending physician reviewing medical charts and radiological and laboratory records. This study analyzes data from the first ICU case until December 31 2009. Children under 15 years old were not enrolled in the study. The study was approved by the ethical board of Joan XXIII University Hospital, Tarragona (Spain). Patients remained anonymous and the requirement for informed consent was waived due to the observational nature of the study. All tests and procedures were ordered by the attending physicians.

Definitions

The following variables were recorded: demographic data, comorbidities, time of illness onset and hospital admission, time to first dose of antiviral delivery, microbiologic findings, and chest radiologic findings at ICU admission. Intubation and mechanical ventilation requirements, adverse events during ICU stay (e.g. need for vasopressor drugs, or renal replacement therapies) and laboratory findings at ICU admission were also recorded. To determine the severity of illness, the Acute Physiology And Chronic Health Evaluation (APACHE) II score [7] was determined in all patients within 24 hours of ICU admission. Organ failure was assessed using the Sequential Organ Failure

Assessment (SOFA) scoring system [8]. Obese patients were defined as those with a body mass index (BMI) over 30 kg/m².

Primary viral pneumonia was defined in patients presenting illness with acute respiratory distress and unequivocal alveolar opacities involving two or more lobes with negative respiratory and blood bacterial cultures during the acute phase of influenza virus [2]. Nasopharyngeal-swab specimens were collected for respiratory viruses at hospital admission. Nasopharyngeal-swab specimens were collected at admission, and lower respiratory secretions were also obtained in intubated patients. Real time polymerase chain reaction (RT-PCR) testing was performed in accordance with the published guidelines from the CDC [9]. Novel influenza A H1N1 testing was performed in each institution or centralized in a reference laboratory when not available. A “confirmed case” was defined as an acute respiratory illness with laboratory-confirmed pandemic H1N1 virus infection identified by real-time RT-PCR or viral culture [10]. Only “confirmed cases” were included in the current study.

Community-Acquired Respiratory Co-infection (CARC) was defined as any infection diagnosed within the first 2 days of hospitalization. Infections occurring later were considered nosocomial [11]. Patients who presented healthcare-associated pneumonia (HCAP) were excluded from the present study [12]. Patients were admitted to the ICU either because they were potential candidates for mechanical ventilation and / or because they were judged to be in an unstable condition requiring intensive medical or nursing care [13, 14].

Oseltamivir was administered orally in accordance with CDC recommendations and the regimen (150mg/24h or 300 mg/24h) was chosen by the attending physician [15]. The

ICU admission criteria and treatment decisions for all patients, including determination of the need for intubation, the dosage of RRT and type of antibiotic and antiviral therapy administered, were not standardized and were decided by the attending physician.

Acute kidney injury (AKI) in critically ill patient affected by pandemic 2009 influenza A (H1N1) virus infection its stages were diagnosed according to the GFR criteria of the current Acute Kidney Injury Network definitions [6]. Information in regard to urine output was not used in the present manuscript. Diagnostic criteria for acute kidney injury (AKI): An abrupt (within 48 hours) reduction in kidney function currently defined as an absolute increase in serum creatinine of more than or equal to 0.3 mg/dl, a percentage increase in serum creatinine of more than or equal to 50% (1.5-fold from baseline), or a reduction in urine output (documented oliguria of less than 0.5 ml/kg per hour for more than six hours) [**Error! Bookmark not defined.**]. Severity of AKI was classified as stage I (serum creatinine increase by >150% to 200% (1.5- to 2-fold) or 0.3 mg/dL), stage II (serum creatinine increase by >200% to 300% (> 2- to 3-fold)) and stage III (serum creatinine increase by > 300% (> 3-fold) or the need for RRT). Alternatively, stage III was defined by an increase of serum creatinine 0.5 mg/dL from baseline serum creatinine values 4.0 mg/dl. The Creatinine criteria describe changes in renal function without specifying the direction of change. We performed an analysis of the maximum AKI severity stage reached. RRT in the course of AKI was always initiated when needed for the following indications: pulmonary oedema, oliguria defined as urine output <0.5 mL/kg body weight per hour for >6 h, metabolic acidosis or hyperkalaemia not responding to conventional treatment and uraemia defined as urea nitrogen of >100 mg/dL. RRT was available 24 h a day and no patient requiring RRT was denied RRT for futility. All pairs of creatinine levels were taken with 48hrs periods

were analyzed during the course of ICU admission as the maximum AKIN stage was used.

Statistical analysis

Discrete variables are expressed as counts (percentage) and continuous variables as means \pm standard deviation (SD) or medians with 25th to 75th interquartile range (IQR). For the demographic and clinical characteristics of the patients, differences between groups were assessed using the chi-squared test and Fisher's exact test for categorical variables and the Student's *t*-test or Mann-Whitney U test for continuous variables. Variables significantly associated with mortality in the univariate analysis were entered in the regression model. In order to avoid spurious associations, variables entered in the regression models were those with a relationship in univariate analysis ($P \leq 0.05$) or a plausible relationship with the dependent variable. Results are presented as Odds ratio (OR) and 95% confidence intervals (CI). Potential explanatory variables were checked for co-linearity prior to inclusion in the regression models using Tolerance and Variance Inflation Factor. Data analysis was performed using SPSS for Windows 15.0 (SPSS, Chicago, IL, US).

Results

A total of 968 patients from 148 Spanish ICUs were included in the database and after excluding patients with chronic kidney disease on dialysis ($n = 48$) and uncompleted data ($n = 259$) a total of 661 patients were analyzed in this study (figure 1). Of these, 364 patients were male (55.1%) with a median age of 43 (IQR 33-53) years, and 581 (87.9%) were under 60 years of age. The mean APACHE II score was 13.6 ± 6.7 and

the mean SOFA score was 5.4 ± 3.4 on admission. Invasive mechanical ventilation (MV) was used in 408 (61.7 %) of the patients. All patients received antiviral therapy. Comorbidities excluding chronic renal failure were present in 466 (70.5 %) patients. Obesity $n = 248$ (37.5%), chronic obstructive pulmonary disease (COPD) $n = 109$ (16.5%) and asthma $n = 87$ (13.2%) were the main comorbidities reported.

One hundred and eighteen (17.7 %) patients developed AKI; Patients with AKI were mostly male (65.3% vs 52.9% $p < 0.01$) and with a mean age of 43.8 ± 14.2 years. Patients with AKI presented comorbidities more frequently than non-AKI patients (77.1% vs 69.1%; $p = 0.05$). Patients with AKI had higher APACHE II (19.1 ± 8.3 vs. 12.6 ± 5.9 , $p < 0.001$), higher SOFA (8.7 ± 4.2 vs. 4.8 ± 2.9 $p < 0.001$), more need of mechanical ventilation (VM) (87.3% vs. 56.2 % $p < 0.01$ OR 5.3 CI 3.0-9.4), more presence of shock (75.4% vs. 38.3% $p < 0.01$ OR 4.9 CI 3.1-7.7), Multiple Organ Dysfunction Score (MODS) (92.4% vs. 54.7% $p < 0.01$ OR 10.0 CI 4.9-20.21) and Community-Acquired Respiratory Co-infection (CARC) (23.7% vs. 14.4% $p < 0.01$ OR 1.8 CI 1.1-3.0) (Table 1). Patients with AKI showed higher C-reactive protein (median 28, IQR 16.8-61.2 versus 20 IQR 12-42.1) mg/dL, $p < 0.01$) and PCT ((median 2, IQR (0.8-10) versus 0.5 IQR (0.1-1.8 ng/mL $p < 0.01$) $p < 0.01$) and CK (median 170, IQR (74-417) vs 290 IQR (92.25-862) $p < 0.01$).

Thirty-seven (31.4%) of the patients with AKI were classified as AKI I, 15 (12.7%) as AKI II and finally 66 (55.9 %) as AKI III, of which 50 (75.7%) required Continuous Renal Replacement Therapy (CRRT). Additional clinical characteristics of patients with pandemic 2009 influenza A (H1N1) v infection in accordance with AKI classification are presented in Table 2.

In survivors, patients with AKI remained longer on MV (13.6 ± 15.2 vs 8.4 ± 11.5 days, $p=0.003$), ICU LOS (19.4 ± 16.5 vs 12.6 ± 13.0 days; $p<0.0001$), hospitalization (30.3 ± 19.9 vs 20.5 ± 16.8 days; $p<0.0001$) than non-AKI patients. (Table 3)

The overall ICU mortality was 18.8 % and this mortality was significantly higher for AKI patients as compared with non-AKI patients (44.1% vs 13.3% $p<0.01$ OR 5.1 CI 3.3-7.9). AKIN categories were classified as 4 mutually exclusive categorical variables. ICU mortality in patients defined by AKIN criteria was as follows: No AKI 13.3%, AKI I 24.3%, AKI II 33.3% and AKI III 57.6%, $p < 0.0001$. (Figure 2). In addition, Table 4 displays that APACHE II, SOFA, invasive mechanical ventilation, shock, MODS, haematology disease and bacterial co-infection were variables associated with ICU mortality (univariate analysis). A logistic regression analysis was performed with previous significantly associated variables from the univariate analysis and with AKIN categories. Multivariate analysis demonstrated that among patients with AKI only AKI III was independently associated with higher ICU mortality (OR=4.81; 95% CI 2.17 – 10.62; $p<0.001$) with a Hosmer-Lemeshow goodness of fit test of 3.44 ($p=0.903$) for the model (Table 5). In addition, with the aim to validate these results and to avoid a survival advantage of patients who died very early after ICU admission, a logistic regression analysis was performed excluding patients who died within the first 48 hours. The result of this analysis was highly consistent to the previous one (OR=5.31; 95% CI 2.37 – 11.91; $p<0.001$).

Discussion

To the best of our knowledge this is the largest study to date focusing on acute kidney injury during the 2009 influenza pandemic. The main finding of the present study was

that the presence of AKI in ICU patients with a severe presentation of 2009 pandemic (H1N1) v Influenza A infection was associated with increased mortality rates. In addition, only AKI III patients who were included shown higher rates and were found to be an independent risk factor for ICU mortality.

Acute Kidney Injury (AKI) is a complex disorder that occurs in a variety of settings with clinical manifestations ranging from a minimal elevation in serum creatinine to anuric renal failure. It is often under-recognized and is associated with severe consequences [16]. Renal impairment is a common situation among ICU patients, and is associated with high mortality rates and consumption resources, especially in patients who require Renal Replacement Therapy (RRT). Recent epidemiological studies demonstrate the wide variation in etiologies and risk factors [17, 18, 19]. AKI occurs in approximately 19 percent of patients with moderate sepsis, 23 percent with severe sepsis, and 51 percent with septic shock [20]. Patients who have sepsis-related AKI have much higher mortality than patients with AKI who do not have sepsis [21]. Ostermann *et al.* [22] have recently demonstrated that the risk of death is higher in patients with a worse degree of AKI and only AKI III was independently associated with ICU mortality.

The mortality in AKI observed in patients affected by pandemic (H1N1) v Influenza A infection H1N1 has been previously reported in other forms of critical illness particularly severe sepsis. Lopes *et al.* [23] conducted a retrospective study of a cohort of 315 patients with sepsis admitted to the infectious diseases ICU, in order to determine the impact of AKI during ICU admission and found that AKI had a negative impact on in-hospital mortality of patients with sepsis. As compared with patients without acute renal impairment, patients with AKI had an increased probability of death of 25.3%. Moreover, the authors found that the AKIN criteria were a useful tool to

characterize and stratify septic patients according to the risk of death. In addition, the cause-and-effect relationship between viral infection and kidney injury is not clear [24]. A cause-and-effect relationship has been inferred from the clinical course in some studies. One possible mechanism is glomerular deposition of viral antigen, which seems to be secondary to the deposition of immune complexes. That is the abnormal expression of cytokine dysregulation associated with severe viral infections injury might contribute to the renal injury of pandemic 2009 influenza A (H1N1) v infection. Bermejo-Martin *et al.* [25] recently reported an early secretion of Th17 and Th1 cytokines in patients with severe pandemic 2009 influenza A (H1N1) v infection. In addition, To *et al.* [26] demonstrated a slower control of viral load in patients with an exuberant cytokine. Increased cytokines together with lymphokines, lead to the adhesion of inflammatory cells to endothelium and other injury sites [27] Endothelium-dependent vasodilation is a prominent feature in patients with moderate renal impairment [28] and plasma cytokine levels could be useful in predicting mortality rates in critically ill patients with AKI.

Pandemic 2009 influenza A (H1N1) v infection is associated with a high fatality rate [1, 2, 3, 4], however a potential explanation for such rates have not been totally elucidated. Patients who required ICU admission have frequently experienced rapidly progressive, serious lower respiratory tract disease. Other well-recognized influenza complications in these seriously ill with pandemic 2009 influenza A (H1N1) v infection have included renal failure, however the exact impact has not been extensively investigated. During the first case reports, impairment of renal function was commonly observed and patients who died had documented multiple organ failure with significantly higher rates of renal failure [29, 30]. Myalgia is usually prominent early in the illness, contrasting with

available descriptions of influenza-associated myositis where onset is after or during resolution of respiratory symptoms. Although direct muscle invasion by the virus is one of the possibilities suggested for virus-related rhabdomyolysis, not all the patients who developed AKI showed high levels of CK. In addition AKI has been reported worldwide during the last pandemic with very different incidence and a paucity of robust AKI definitions. Data from Chile reported a 25 % incidence manifested an elevated Creatinine levels. Sood *et al.* [31] in a cohort of 50 critically ill patients and Trimarchi *et al.* [32] in 22 patients reported an incidence around 65%. In our study, 17.7% of patients developed AKI. Differences with other studies might be related to our critically ill population where the criteria was standardized and based on AKIN criteria. Finally, mortality rates of 16, 19 and 54% respectively have been reported among critically ill patients affected by pandemic 2009 influenza A (H1N1) v infection in Brazil [33], Argentina [5] and Canada [3]. The main difference is that in the present study although the mortality was 18.8 % and significantly higher for patients who developed AKI, a multivariate analysis demonstrated that only the stage AKINIII was independently associated with ICU mortality.

The present study presented some limitations that should be addressed. First, this is an observational, non interventional study in which 148 ICUs were self-selected. Management of patients was not standardized and management practices were chosen in accordance with local protocols. Nevertheless, it presented the strength of a prospective nature, multicentre and with a large number of patients. Secondly, in the present study notes review to check for context of clinical presentation and fluid resuscitation was not employed. In addition, the information in regard to urine output and estimated baseline creatinines was not used; this was the reason for choice of this system based on AKIN

criteria instead of other system of classification of AKI such as RIFLE [34, 35]. The degree of AKI classified by both RIFLE and AKIN criteria correlates with mortality in a progressive fashion, emphasizing the importance of the severity of AKI. Both classification systems help to standardize the definition and management of AKI. In the present analysis AKIN criteria was chosen for analysis instead of RIFLE. The choice of AKIN criteria may have been driven by the lack of reliance on baseline creatinine. RIFLE does not take into consideration the nature or site of the kidney injury [36]. Finally, a potential bias might be incurred because a diagnosis of AKI as a baseline hazard ignores some patients that may die very early before a diagnosis of AKI can be made. In order to avoid this potential bias the multivariate analysis was performed after excluding patients who died within the first 48 hours and confirmed that AKI III was associated with a statistically significant worse outcome. In addition, and as it has been reported by other authors [21], some patients using CRRT were classified would have been classified as having AKI I or II and might have altered their outcome. Future research seems mandatory in order to clarify the complexities and confounding factors of AKI.

Conclusions

In summary, AKI represented a frequent complication in critically ill patients affected by pandemic 2009 influenza A (H1N1) v infection and was associated with increased mortality, however only stage AKI III was independently associated with worse outcome. In addition, AKI was associated with increased health care resources manifested by increased ICU and hospital LOS and more days under mechanical ventilation.

Key messages

- AKI represents a frequent complication in critically ill patients affected by pandemic 2009 influenza A (H1N1) v infection.
- AKI development in critically ill patients affected by pandemic 2009 influenza A (H1N1) v infection is associated with worse outcome
- Only critically ill patients affected by pandemic 2009 influenza A (H1N1) v infection in stage AKI III are independently associated with increased mortality.
- AKI development in critically ill patients affected by pandemic 2009 influenza A (H1N1) v infection is associated with increased health care resources manifested by increased ICU and hospital LOS and more days under mechanical ventilation.
- Supportive measure should be warranted promptly in order to decrease the development of AKI in Critically ill patients affected by pandemic 2009 influenza A (H1N1) v infection.

Abbreviations

AKI: Acute Kidney Injury, AKIN: Acute Kidney Injury Network, APACHE: Acute Physiology And Chronic Health Evaluation, BMI: body mass index, CAP: community-acquired pneumonia, CDC: Centre Disease Control, CI: confidence intervals, CK: Creatine Kinase, COPD: chronic obstructive pulmonary disease, CRP: C-Reactive Protein, CRRT: Continuous Renal Replacement Therapy, GFR: Glomerular Filtration Renal, HCAP: healthcare-associated pneumonia, HIV: Human Immunodeficiency virus, HR hazard ratio, ICU: Intensive Care Unit, IQR: interquartile range, OR: Odds Ratio, LOS: Length of stay, MODS: Multi-organ Dysfunction Syndrome, MV: Mechanical Ventilation, PCT: Procalcitonine, RIFLE: Risk, Injury, Failure, Loss, ESKD (End Stage Kidney Disease), RRT: Renal Replacement Therapy, RT-PCR: Real time polymerase chain reaction, S: Stage, SD: standard deviation, SOFA: Sequential Organ Failure Assessment, WHO: World Health Organization.

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

AR made a substantial contribution. AR and IML assisted in the design of the study, coordinated patient recruitment, analysed and interpreted the data, and assisted in writing the paper. RZ, RG, LS, JB, MV, JCP, PL, JJ-N, MLC and AA made an

important contribution to acquisition and analysis of data. EP and DS were involved in revising the manuscript critically for important intellectual content. JR and ED made a substantial contribution to the conception, design, analysis and interpretation of data, and revised the final manuscript version. All authors read and approved the final manuscript.

Acknowledgements

We are indebted to David Suárez for statistical support. This research was supported by Agència de Gestió d'Ajuts Universitaris i de Recerca (AGAUR) (2009/SGR/1226).

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Figure legends

Figure 1. Flow chart of critically ill patients enrolled in the study with 2009 Pandemic Influenza A (H1N1) virus infection.

Figure 2. Intensive Care Unit mortality among patients with pandemic 2009 influenza A (H1N1) virus infection and AKIN criteria.

Table 1. Comparison of baseline characteristics for patients with or without AKI in patients affected by pandemic 2009 influenza A (H1N1) v infection.

Variables	Non- AKI <i>n</i> = 543	AKI <i>n</i> = 118	Total <i>n</i> = 661	<i>P</i>
Age, years	43.5(13.9)	44.9(15.2)	43.8(14.2)	0.3
Male sex <i>n</i> (%)	288(53%)	77(65.3%)	365(55.2%)	0.01
Comorbidities <i>n</i> (%)				
Pregnancy	34(6.3%)	5(4.3%)	39(5.9%)	0.5
COPD	90(16.5%)	19(16.2%)	109(16.5%)	0.9
Asthma	76(14.0%)	11(9.4%)	87(13.2%)	0.2
Heart failure	29(5.3%)	10(8.5%)	39(5.9%)	0.2
Obesity	196(36.0%)	52(44.4%)	248(37.5%)	0.09
Diabetes	52(9.6%)	19(16.2%)	71(10.7%)	0.04
Immunosuppression	17(3.1%)	3(2.6%)	20(3.0%)	0.9
Hematologic disease	26(4.8%)	8(6.8%)	34(5.1%)	0.3
Neuromuscular disease	21(3.9%)	2(1.7%)	23(3.5%)	0.4
HIV infection	12(2.2%)	3(2.6%)	15(2.3%)	0.7

AKI acute kidney injury; COPD Chronic obstructive pulmonary disease; HIV human immunodeficiency virus.

Table 2. Selected Physiologic and laboratory Characteristics of patients with pandemic 2009 influenza A (H1N1) virus infection with or without AKI and AKIN criteria.

Variables	TOTAL	Non AKI n = 543	AKI n = 118	P	Non AKI n = 543	AKI I n = 37	AKI II n = 15	AKI III n = 66	P
APACHE II score.	13.6(6.7)	12.6(5.9)	19.1(8.4)	<0.001	12.6(5.9)	16.6(6.9)	20.9(7.4)	20.8(9.3)	<0.001
Mean (SD)									
SOFA score.	5.4(3.5)	4.8(2.9)	8.7 (4.2)	<0.001	4.8(2.9)	4.7(2.9)	7.7(3.5)	9.2(4.4)	<0.001
Mean (SD)									
Invasive MV n (%)	408(61.7%)	305(56.2%)	103(87.3%)	<0.001	305(56.2%)	28(75.7%)	12(80.0%)	63(95.5%)	<0.001
Shock n (%)	297(44.9%)	208(38.3%)	89(75.4%)	<0.001	208(38.3%)	23(62.2%)	8(53.3%)	58(87.9%)	<0.001
MODS n (%)	406(61.4%)	297(54.7%)	109(92.4%)	<0.001	297(54.7%)	29(78.4%)	14(93.3%)	66(100.0%)	<0.001
Coinfection n (%)	106(16.0%)	78(14.4%)	28(23.7%)	<0.01	78(14.4%)	10(27.0%)	5(33.3%)	13(19.7%)	0.03
Laboratory findings median (IQR)									
Leukocyte count (per mm3)	6900(4000-11500)	6800(3925-11075)	8300(4300-14000)	<0.01	6800(3925-11075)	6770(4250-15850)	8850(4375-11525)	8200(4200-13750)	0.5
Platelets count (per mm3)	163.5(120-223.2)	166(124-227)	149(99-197)	0.09	166(124-227)	160(110-238)	140(81-181)	149(77.5-197.5)	0.02
Serum creatine kinase (U/L)	176.5(75-474.2)	170(74-417-75)	290(92.25-862)	<0.01	170(74-417)	199(36-1270)	218(48-475)	319(136.5-860.25)	0.005
Serum lactate dehydrogenase(IU/L)	611(366.510-19.7)	600(355-986)	720(402-1103)	0.001	600(355-986)	506(305-954)	380(338-439)	1000(606-1527)	<0.001
SerumAST (IU/L)	53(32-99)	50(31.25-88.75)	64(36.5-147)	0.001	50(31.25-88.75)	47(29.5-111)	120(48.5-204)	75(50-176)	<0.001
Serum ALT (U/L)	39.5(23-78)	38(23-76)	49.5(26-96.75)	0.001	38(23-76)	52.5(24.75-83.5)	46.5(22.5-89.5)	48.5(26.5-129.75)	0.1
PCT(ng/ml)	0.59(0.1-2.1)	0.5(0.1-1.8)	2(0.8-10)	0.001	0.5(0.1-1.8)	2(0.57-5.72)	8.3(3.7-10.0)	2(0.7-6.9)	<0.001
CRP(mg/ml)	21.1(12.2-44.8)	20(12-42.1)	28(16.8-61.2)	<0.01	20(12-42.1)	34(16.1-63.7)	29(8.6-44.6)	25.8(19.2-69)	0.08

AKI acute kidney injury; APACHE acute physiology and chronic health evaluation; SOFA sequential organ failure assessment; MV mechanical ventilation; MODS multi-organ dysfunction syndrome; LOS length of stay; ICU intensive care unit; PCT procalcitonine; CRP C-Reactive protein.

Table 3. Outcomes of patients with pandemic 2009 influenza A (H1N1) v infection.

with or without AKI and AKIN criteria.

Variables	Non AKI <i>n</i> = 543	AKI <i>n</i> = 118	<i>P</i>	Non AKI <i>n</i> = 543	AKI I <i>n</i> = 37	AKI II <i>n</i> = 15	AKI III <i>n</i> = 66	Total	<i>P</i>
ICU death	72(13.3%)	52(44.1%)	<0.001	72(13.3%)	9(24.3%)	5(33.3%)	38(57.6%)	124(18,8%)	<0.001
MV days ^a									
Mean (SD)	8.4(11.5)	13.6(15.2)	<0.001	8.4(11.5)	13.3(17.6)	9.3(11.8)	16.4(12.5)	9.0(12.0)	0.01
Median (IQR)	4(0-12)	10(3.75-21.5)		4(0-12)	8(3.25-20.75)	5(0-14.5)	15(5.5-26.5)	5(0-13)	
LOS ICU ^b									
Mean (SD)	12.6(13)	19.4(16.5)	<0.001	12.6(1)	19.6(18.4)	13.4(11.5)	22.1(15.3)	13.4(13.6)	<0.001
Median (IQR)	8(4-17)	13(7-30)		8(4-17)	12(7-29.5)	8(5.5-19.5)	21.5(7.75)	9(4-18)	
LOS Hospital ^b									
Mean (SD)	20.5(16.8)	30.3(19.9)	<0.001	20.5(16.8)	29.3(21.4)	23.0(14.7)	36.0(19.0)	21.6(17.5)	<0.001
Median (IQR)	15(9-27))	26.5(13.75- 44.25)		15(9-27)	24.5(13-44.5)	20(10-34.5)	35(19.5-49)	16(9-29)	

^aOnly survivors and mechanically ventilated. ^bOnly survivors.

AKI acute kidney injury; ICU intensive care unit; MV mechanical ventilation; LOS length of stay.

Table 4. Comparison of demographic and clinical characteristics among with pandemic 2009 influenza A (H1N1) virus infection.

Variables	Survivors <i>n</i> = 527	Non survivors <i>n</i> = 134	<i>P</i>
Age, years. Mean (SD)	43.2(13.9)	46.09(15.2)	0.1
Male sex <i>n</i> (%)	290(54.0%)	74(59.7%)	0.2
APACHE II score, Mean (SD)	12.5(5.9)	18.8(7.9)	<0.001
SOFA score, Mean (SD)	4.8(2.8)	8.1(4.3)	<0.001
Comorbidities <i>n</i> (%)			
Pregnancy	33(6.1%)	6(4.8%)	0.6
COPD	94(17.5%)	15(12.1%)	0.1
Asthma	76(14.2%)	11(8.9%)	0.1
Heart failure	28(5.2%)	11(8.9%)	0.1
Obesity	194(36.1%)	54(43.5%)	0.1
Diabetes	56(10.4%)	15(12.1%)	0.6
Immunosuppression	13(2.4%)	7(5.6%)	0.07
Hematological disease	19(3.5%)	15(12.1%)	<0.001
Neuromuscular disease	17(3.2%)	6(4.8%)	0.4
HIV infection	11(2.0%)	4(3.2%)	0.4
Invasive MV	290(54.0%)	118(95.2%)	<0.001
Shock	208(38.7%)	89(71.8%)	<0.001
MODS	299(55.7%)	107(86.3%)	<0.001
Co-infection	76(14.2%)	30(24.2%)	<0.01

Survivors vs. Non survivors. AKI acute kidney injury; APACHE acute physiology and chronic health evaluation; SOFA sequential organ failure assessment; COPD chronic obstructive pulmonary disease; HIV human immunodeficiency virus; MV mechanical ventilation; MODS multi-organ dysfunction syndrome.

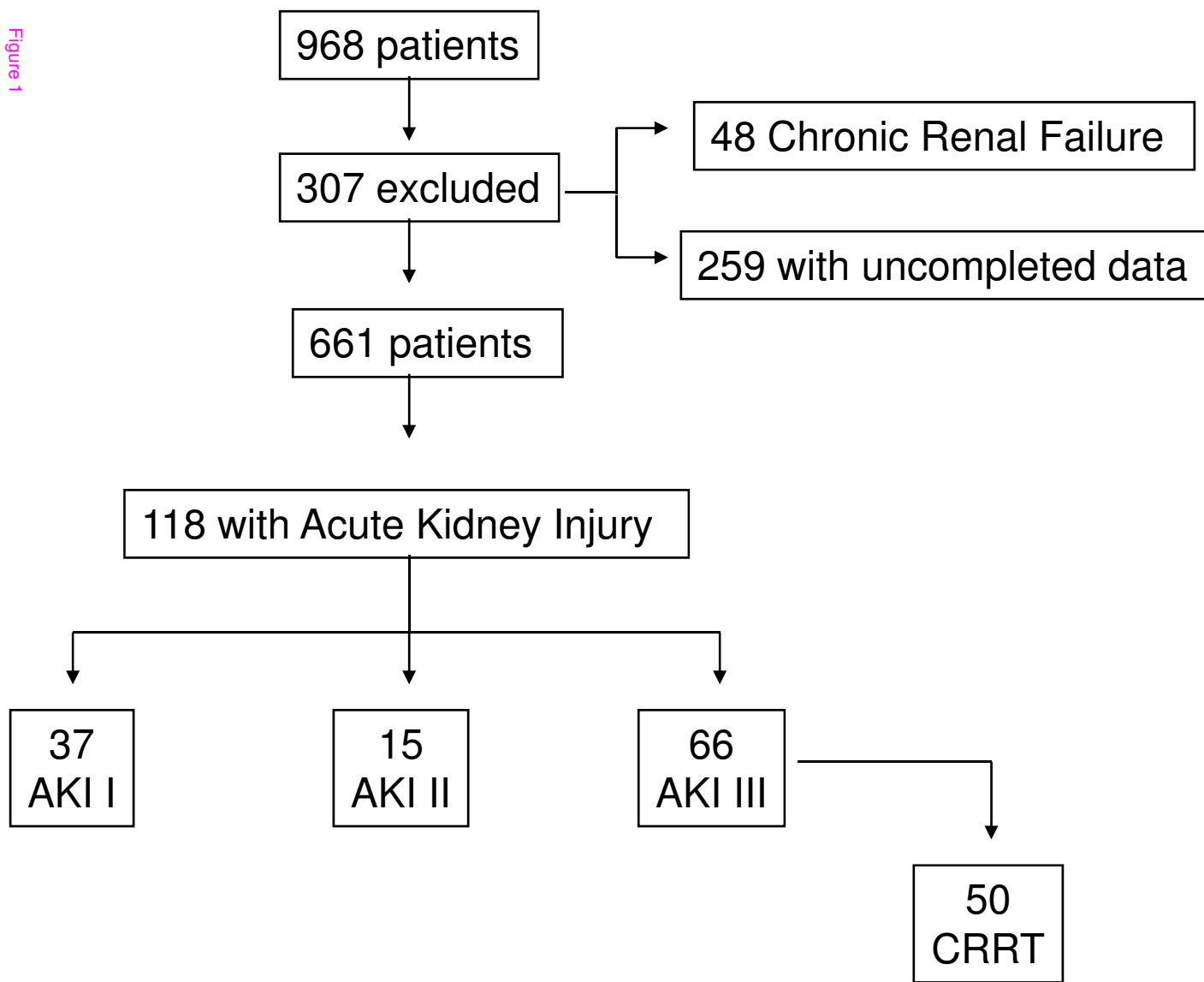
Table 5. Multivariate logistic regression analysis: risk factors for ICU mortality base on AKI criteria.

Variables	B	Wald	P	OR	95% CI
AKI					
AKI I	0.42	0.79	0.37	1.52	0.61-3.81
AKI II	0.61	0.81	0.36	1.83	0.48-6.90
AKI III	1.57	15.06	0.000	4.81	2.17-10.62
APACHE II	0.05	5.87	0.01	1.06	1.01-1.11
Constant	-5.19	60.58	0.00	0.00	

AKI acute kidney injury; APACHE acute physiology and chronic health evaluation; OR odds ratio; CI confidence intervals.

Additional files

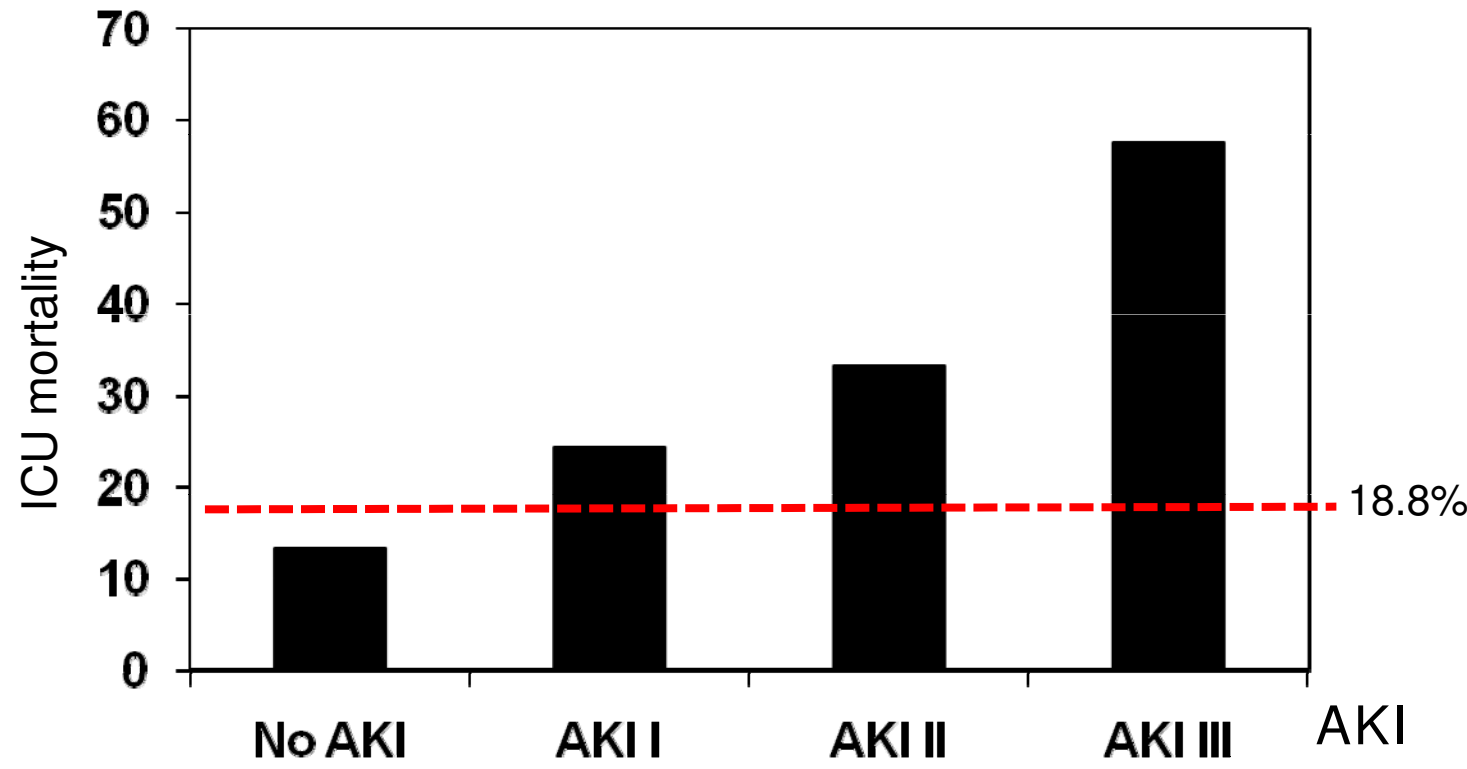
Additional file 1. H1N1 SEMICYUC Working Group investigators.



AKI Stage: Mortality rate

Figure 2

661 patients with 2009 H1N1 v



Additional files provided with this submission:

Additional file 1: Additional file 1.docx, 20K

<http://ccforum.com/imedia/1792439557520708/supp1.docx>