Cystatin C: a potential predictor for acute kidney injury in patients with community acquired pneumonia

Xin Wan (wanxin@njmu.edu.cn)
Nanjing First Hospital, Nanjing Medical University

Dawei Chen
Nanjing First Hospital, Nanjing Medical University

Linglin Jiang
Nanjing First Hospital, Nanjing Medical University

Mengqing Ma
Sir Run Run Hospital, Nanjing Medical University

Wenjuan Huang
Nanjing First Hospital, Nanjing Medical University

Yan Tan
Nanjing First Hospital, Nanjing Medical University

Xiaobing Ji
Nanjing First Hospital, Nanjing Medical University

Binbin Pan
Nanjing First Hospital, Nanjing Medical University

Research Article

Keywords: Cystatin C, biomarker, acute kidney injury, community acquired pneumonia

Posted Date: April 27th, 2022

DOI: https://doi.org/10.21203/rs.3.rs-1267123/v2

License: This work is licensed under a Creative Commons Attribution 4.0 International License. Read Full License
Abstract

**Background:** Acute kidney injury (AKI) is common in patients with community acquired pneumonia (CAP), and associated with poor prognosis. Cystatin C had been demonstrated to be a biomarker for the early detection AKI in several other clinical settings. Therefore, in this study we evaluated whether AKI in patients with CAP could be well predicted by serum Cystatin C within 24 hours after admission.

**Methods:** Univariate and multivariate logistic regression analyses were used to investigate independent factors of AKI in patients with CAP. Prediction performance of all independent factors for AKI was measured using area under the receiver operating characteristic (ROC) curves (AUCs).

**Results:** 2716 patients with CAP were eligible in this study, and 766 (28%) patients developed AKI. After multivariate logistic regression analysis, Cystatin C, albumin, uric acid, platelet count, white blood cell count, CURB-65 score, and acute respiratory failure were independent factors for AKI in patients with CAP. The maximum AUC was reported for serum Cystatin C within 24 hours after admission. Cystatin C had an AUC of 0.81 (95% CI: 0.79–0.83, \( P < 0.001 \)) for predicting AKI, with an optimal cut-off value of 1.37 mg/L, computing 68% sensitivity, 80% specificity, 57% positive predictive value and 86% negative predictive value. In the stratification analyses, Cystatin C still had a good performance for predicting AKI in all the subgroups (AUCs: 0.69-0.84).

**Conclusions:** The level of serum Cystatin C within 24 hours after admission appears to be a good biomarker for predicting of AKI in patients with CAP.

**Background**

Community acquired pneumonia (CAP) is responsible for substantial mortality, with a third of patients dying within 1 year after being discharged from hospital for pneumonia[1]. Acute kidney injury (AKI) is a common complication of CAP, with the incidence rates from 18 to 34% [2–4]. Moreover, AKI is associated with a poor prognosis in patients with CAP [2, 3, 5, 6]. Lakhmir S. et al. found that patients who were admitted to hospital for pneumonia and developed AKI had a poor effect on long-term prognosis. They were at high risk for death, dialysis, and permanent loss of renal function [6]. Even among patients diagnosed with non-severe pneumonia, AKI could increase higher long-term mortality risk [3]. Recently, our team also found that patients with CAP who developed AKI had worse short-term prognosis. They were more likely to require admission to intensive care unit, mechanical ventilation, invasive mechanical ventilation, non-invasive mechanical ventilation, had higher in-hospital mortality, and experienced a longer duration of hospital stay [5].

Previous study showed that Cystatin C was a good biomarker in the prediction of AKI in other clinical settings [7], as it was not influenced by age, gender, race, muscle mass, and protein intake [8]. However, few studies explored the prediction efficiency of Cystatin C for AKI in patients with CAP. Therefore, in this study we evaluated whether AKI in patients with CAP could be well predicted by serum Cystatin C within 24 hours after admission.
Methods

Patient selection

This retrospective study was approved by the Nanjing First Hospital Institutional Review Board and patients' informed consent was waived due to the retrospective nature of the study. This study was conducted according to the guidelines of the Declaration of Helsinki. We reviewed the medical records of 5851 patients, who were ≥ 18 years of age and admitted to hospital for CAP at Nanjing First Hospital from January 2014 to May 2017. Exclusion criteria were as follows: patients without Cystatin C, patients with less than two repeated serum creatinine (SCr), patients with a history of end stage renal disease or requiring dialysis, and patients lacking complete medical records. Finally, 2716 patients were enrolled in this study. (Fig. 1)

Definitions of CAP and AKI

Pneumonia diagnosed based on detection of interstitial infiltrate changes on chest radiography or CT in patients with one or more of: (a) recent presence of dyspnea, cough, or sputum; (b) core body temperature > 38.0°C; or (c) peripheral white blood cell > counts 10 × 10^9/L or < 4 × 10^9/L. In addition, illness onset was specifically in the community, rather than in the health-care setting [9, 10].

The definition of AKI in our study adhered to the Kidney Disease Improving Global Outcomes (KDIGO) criteria, which defined AKI as an increase in SCr levels by ≥ 1.5-fold from baseline within 7 days of illness onset or an increase in SCr levels by ≥ 0.3 mg/dL (26.4 µmol/L) within 24 h of illness onset [11]. Baseline SCr values were defined as the lowest levels measured during hospitalization. Due to the lack of data concerning urine output, urine output standards were not considered in this study.

Data Collection

Demographics (gender and age), comorbid conditions (hypertension, diabetes mellitus, coronary artery disease, cardiac insufficiency, atrial fibrillation, chronic obstructive pulmonary disease [COPD], chronic kidney disease, pulmonary hypertension, cerebrovascular diseases, and tumour), complication (acute respiratory failure [12]), severity scoring on admission (confusion, uremia, respiratory rate, blood pressure, and age 65 years or older [CURB-65]) [13], and laboratory tests (albumin, uric acid, Cystatin C, hemoglobin, platelet count, and white blood cell count) within 24 hours after admission were collected from the hospital records.

Data Analysis

Baseline characteristics were presented as means ± SDs or medians and interquartile ranges for continuous variables if appropriate, and proportions for categorical variables. Students’ t tests or Mann-Whitney test were used to compare continuous variables between groups. Chi-square tests or Fisher exact were conducted to tell the differences of categorical variables between groups.
Univariate and multivariate logistic regression analysis was used to identify independent risk factors of AKI through stepwise selection. Prediction performance of all independent factors for AKI was measured using area under the receiver operating characteristic (ROC) curves (AUCs). We found that the maximum AUC was reported for serum Cystatin C within 24 hours after admission. To determine the optimal cut-off value for Cystatin C in discriminating AKI, we estimated the Youden index.

As a stratification analyses to evaluate the performance of serum Cystatin C within 24 hours after admission for predicting AKI in various subgroups, we conducted multivariate logistic regression analysis to explore whether Cystatin C was still an independent predictor for AKI in various subgroups. The various subgroups were classified by age, gender, comorbidities (hypertension, diabetes, coronary artery disease, cardiac insufficiency, cerebrovascular disease, atrial fibrillation, COPD, chronic kidney disease, and tumour), laboratory investigations (albumin, anemia [for male, hemoglobin < 120 g/L; for female, hemoglobin < 110 g/L] [14], platelet count, white blood cell count, and uric acid), CURB-65 Score, and complication (acute respiratory failure). Stratification analyses adjusted for all above factors except the stratification factor itself. For the subgroups of intensive care unit (ICU) admission, and mechanical ventilation, stratification analyses adjusted for all above factors (demographics, comorbid conditions, complication, and laboratory investigations). Furthermore, prediction performance of Cystatin C for AKI was also measured by AUCs in various subgroups. P values < 0.05 were considered as statistically significant. Statistical analysis was using SPSS software version 22 (IBM, Armonk, NY, USA), the EmpowerStats (www.empowerstats.net, X&Y solutions, Inc. Boston MA) and R version 3.6.1 (http://www.r-project.org).

Results

Patient characteristics

Totally, 2716 patients were eligible in this study. The mean (median, range) age of the patients was 71.6 (75, 63–83) years and most of the study population consisted of males (60.9%). 487 (17.9%) patients complicated with acute respiratory failure. 447 (16.5%) patients required mechanical ventilation, and 597 (22.0%) patients needed admission to ICU.

AKI characteristics

766 (28%) patients developed AKI. The characteristics of patients with AKI were shown in Table 1. Compared with non-AKI group, male gender (67.2% versus 58.4%; \( P < 0.001 \)) and older age (78.2 years versus 69.0 years; \( P < 0.001 \)) had significant difference between the two groups. Hypertension, diabetes mellitus, coronary artery disease, cardiac insufficiency, atrial fibrillation, chronic kidney disease, and cerebrovascular diseases were more common in the AKI group. However, no statistically significant comorbidities were in COPD, pulmonary hypertension, and tumour between the two groups. Patients in the AKI group were more commonly complicated with acute respiratory failure (39.2% versus 9.6%; \( P < 0.001 \)), and had a higher CURB-65 score than the no-AKI group. In addition, patients with AKI had higher
levels of uric acid, Cystatin C, and white blood cell count, while they had lower levels of albumin, hemoglobin, and platelet count.

Table 1

Patients baseline in patients with and without acute kidney injury
| Variables                  | All (n = 2716) | Non-AKI (n = 1950) | AKI (n = 766) | P Value |
|----------------------------|----------------|-------------------|---------------|---------|
| **Demographics**           |                |                   |               |         |
| Gender (male), n (%)       | 1653 (60.9)    | 1138 (58.4)       | 515 (67.2)    | <0.001  |
| Age (years)                | 71.6 ± 15.8    | 69.0 ± 16.2       | 78.2 ± 12.3   | <0.001  |
| **Comorbid conditions, n (%)** |            |                   |               |         |
| Hypertension               | 1380 (50.8)    | 903 (46.3)        | 477 (62.3)    | <0.001  |
| Diabetes mellitus          | 553 (20.4)     | 346 (17.7)        | 207 (27.0)    | <0.001  |
| Coronary artery disease    | 779 (28.7)     | 481 (24.7)        | 298 (38.9)    | <0.001  |
| Cardiac insufficiency      | 618 (22.8)     | 335 (17.2)        | 283 (36.9)    | <0.001  |
| Atrial fibrillation        | 317 (11.7)     | 182 (9.3)         | 135 (17.6)    | <0.001  |
| COPD                       | 336 (12.4)     | 234 (12.0)        | 102 (13.3)    | 0.349   |
| Chronic kidney disease     | 184 (6.8)      | 71 (3.6)          | 113 (14.8)    | <0.001  |
| Pulmonary hypertension     | 87 (3.2)       | 57 (2.9)          | 30 (3.9)      | 0.186   |
| Tumour                     | 238 (8.8)      | 159 (8.2)         | 79 (10.3)     | 0.073   |
| Cerebrovascular diseases   | 883 (32.5)     | 535 (27.4)        | 348 (45.4)    | <0.001  |
| **Complication**           |                |                   |               |         |
| Acute respiratory failure  | 487 (17.9)     | 187 (9.6)         | 300 (39.2)    | <0.001  |
| **Severity scoring**       |                |                   |               |         |
| CURB-65 scores             |                |                   |               | <0.001  |
| 0                          | 587 (21.6)     | 561 (28.8)        | 26 (3.4)      |         |
| 1                          | 1211 (44.6)    | 916 (47.0)        | 294 (38.6)    |         |
| 2                          | 741 (27.3)     | 416 (21.3)        | 323 (42.4)    |         |
| ≥ 3                        | 177 (6.5)      | 56 (2.9)          | 121 (15.8)    |         |
| **Laboratory tests**       |                |                   |               |         |
| Albumin (g/L)              | 33.2 ± 5.3     | 34.2 ± 4.8        | 30.7 ± 5.4    | <0.001  |
| Uric acid (umol/L)         | 257 (186–360)  | 239 (178–314)     | 345 (228–477) | <0.001  |
| Cystatin C (mg/L)          | 1.3 ± 0.7      | 1.1 ± 0.4         | 1.9 ± 0.9     | <0.001  |
| Hemoglobin (g/L)           | 118.4 ± 21.6   | 121.3 ± 19.5      | 111.0 ± 24.8  | <0.001  |
Platelet count (10^9/L) 198 (148–255) 188 (147–228) 155 (121–203) <0.001

White blood cell count (10^9/L) 7.4 (5.5–10.1) 6.9 (5.3–9.2) 8.8 (6.2–12.7) <0.001

Abbreviation: AKI = acute kidney injury; COPD = chronic obstructive pulmonary disease; CURB-65 = confusion, urea nitrogen, respiratory rate, blood pressure, and age ≥ 65 years.

Independent factors for AKI

Multivariate logistic regression analysis revealed that Cystatin C (OR 4.27, 95% CI 3.36–5.44; P < 0.001), acute respiratory failure (OR 3.96, 95% CI 2.29–3.83; P < 0.001), albumin (OR 0.91, 95% CI 0.89–0.94; P < 0.001), uric acid (OR 1.002, 95% CI 1.001–1.003; P < 0.001), platelet count (OR 0.997, 95% CI 0.996–0.998; P = 0.001), white blood cell count (OR 1.08, 95% CI 1.05–1.10; P < 0.001), and CURB-65 score were independent factors for AKI in patients with CAP. (Table 2)

Table 2

| Variable                          | OR      | 95% CI    | P Value |
|-----------------------------------|---------|-----------|---------|
| Cystatin C (mg/L)                 | 4.27    | 3.36–5.44 | < 0.001 |
| Albumin (g/L)                     | 0.91    | 0.89–0.94 | < 0.001 |
| Uric acid (umol/L)                | 1.002   | 1.001–1.003 | < 0.001 |
| Platelet count (10^9/L)           | 0.997   | 0.996–0.998 | 0.001   |
| White blood cell count (10^9/L)   | 1.08    | 1.05–1.10 | < 0.001 |
| CURB-65 scores                    |         |           |         |
| 0                                 | Reference |         |         |
| 1                                 | 3.03    | 1.82–5.05 | < 0.001 |
| 2                                 | 4.10    | 2.38–7.08 | < 0.001 |
| ≥ 3                               | 7.14    | 3.74–13.62 | < 0.001 |
| Acute respiratory failure         | 2.96    | 2.29–3.83 | < 0.001 |

Abbreviation: AKI = acute kidney injury; CAP = community acquired pneumonia; OR = odds ratio; CI = confidence interval; CURB-65 = confusion, urea nitrogen, respiratory rate, blood pressure, and age ≥ 65 years.

Prediction efficiency of Cystatin C for AKI in patients with CAP
We performed ROC analysis for all independent factors for AKI to determine their prediction performance, respectively. Figure 2 showed the comparisons of AUCs for all independent factors of AKI in patients with CAP. The maximum AUC was reported for serum Cystatin C within 24 hours after admission. Table 3 presented the accuracy of serum Cystatin C for detecting AKI in patients with CAP. Cystatin C had an AUC of 0.81 (95% CI: 0.79–0.83, \( P < 0.001 \)) for predicting AKI, with an optimal cut-off value of 1.37 mg/L, computing 68% sensitivity, 80% specificity, 57% positive predictive value and 86% negative predictive value.

| AUC 95% CI          | Cut-off point | Sensitivity | Specificity | Accuracy | PPV | NPV |
|----------------------|--------------|-------------|-------------|----------|-----|-----|
| 0.81 95% (0.79-0.83) | 1.37 mg/L    | 68%         | 80%         | 77%      | 57% | 86% |

**Abbreviation:** AKI = acute kidney injury; CAP = community acquired pneumonia; AUC = area under the receiver operating characteristic curve; CI = confidence interval; PPV = positive predictive value; NPV = negative predictive value.

**Subgroup analysis**

In the stratification analyses, serum Cystatin C within 24 hours after admission was still an independent predictor in all the various subgroups. Figure 3 showed the ORs, AUCs, cut-off values, sensitivity, and specificity of Cystatin C in all the different subgroups. Moreover, Cystatin C still had a good performance for predicting AKI in all the subgroups (AUCs: 0.69-0.84).

**Discussion**

Previously, Cystatin C had been demonstrated to be a biomarker for the early detection AKI in in other clinical settings, such as patients with traumatic brain injury, neonates, patients with cardiac surgery, patients with liver, and so on [7, 15–18]. To our best knowledge, this present study is the first time to investigate the prognostic value of serum Cystatin C within 24 hours after admission for predicting AKI in the context of CAP with large samples, and it indeed proved to be a good predictor of AKI in patients with CAP.

In this study, the incidence rate of AKI was 28%. Previous studies had demonstrated similar incidence rates of AKI in patients with CAP, ranging from 18 to 34% [2–4]. We found that Cystatin C was an important independent factor for predicting AKI in patients with CAP. Cystatin C is a 13 kilo Dalton proteinase inhibitor, and it is a member of the cystatin super family of cysteine protease inhibitors, which play an important role in intra-cellular catabolism of proteins and peptides [19]. It is synthesized and released into plasma by all nucleated cells at a constant rate [20]. Cystatin C can be more than 99% freely filtered through glomeruli, and do not show significant protein binding. It is considered to be neither
actively secreted into the tubular lumen nor reabsorbed into the plasma. After filtration, it is normally completely reabsorbed by proximal renal tubular epithelial cells, and catabolized by megalin receptor-induced endocytosis [21]. In addition, unlike SCr, the level of serum Cystatin C is not affected by age, sex, body muscle mass, and diet [7]. Therefore, Cystatin C is considered as a good biomarker for the early detection of AKI. In our study, AUC of serum Cystatin C level to predict AKI was 0.81 (95% CI, 0.79–0.83), with an optimal cut-off value of 1.37 mg/L, computing 68% sensitivity, 80% specificity, 57% positive predictive value and 86% negative predictive value. Recently, Cigdem et al. found that serum Cystatin C showed a good predictive power for AKI in patients with COVID-19. The AUC value of serum Cystatin C to predict COVID-19 related AKI was 0.96 (0.90 to 1.0), with the best cut-off value of 1.00 mg/L [22]. Albina et al. previously investigated the potential of plasma N-terminal prohormone B-type natriuretic peptide (NT-proBNP), mid-regional pro-atrial natriuretic peptide (MR-proANP) and B-type natriuretic peptide (BNP) levels to predict early AKI in hospitalized patients with CAP. The AUCs for the prediction of AKI of NT-proBNP, MR-proANP and BNP were 0.79, 0.79, and 0.74, respectively [23]. The strength of this study was that we found Cystatin C also showed good prediction efficiency for AKI in various subgroups (AUCs: 0.69–0.84). Interestingly, it seemed that Cystatin C had slightly better performance for predicting AKI in the subgroups of the non-elderly, female, patients without comorbidities, and patients without serious condition.

In this study, we found that albumin, uric acid, platelet count, white blood cell count, CURB-65 score, and acute respiratory failure were also independent factors for AKI in patients with CAP. CURB-65 [13] and the pneumonia severity index (PSI) [24] were two scoring systems that assessed the severity of CAP. Ahsan R et al. had reported that PSI was an important factor for predicting AKI in patients with CAP [2]. In our study, we found CURB-65 was also an independent risk factor to develop AKI in patients with CAP. Low albumin level had been reported that it was a modifiable risk factor linked to increased risk of AKI in different clinical settings [25]. Recently, a study found that hypoalbuminemia was independently associated with the occurrence of AKI in COVID-19 patients with acute respiratory distress syndrome [26]. Albumin could improve renal perfusion and glomerular filtration through inhibiting apoptosis in renal tubular cells by carrying protective lysophosphatidic acid and scavenging reactive oxygen species [27]. Albumin could prolong potent renal vasodilation, which was induced by serum albumin reacting with the oxides of nitrogen to form S-nitroso-albumin [28]. In addition, several studies suggested that exogenous albumin administration was beneficial to protect the kidneys from AKI [29, 30]. Hyperuricemia was associated with AKI in various statuses [31]. A recent report showed that serum uric acid was an independent predictor of AKI in patients with COVID-19 [32]. Platelet count and white blood cell count were two biomarkers for AKI, and low level of platelet count and high level of white blood cell count could increase risk of AKI [33–36], which was consistent with our findings.

We acknowledge several limitations. First, it is a retrospective single-center study, and the conclusion will need to be confirmed by a multicenter prospective study with a larger patient cohort. AKI is defined according the KDIGO criteria, based on SCr and urine output [11]. However, the urine output data could not be obtained. Therefore, our analysis lacks the urine output standard for AKI.
In summary, AKI is common in patients with CAP. The level of serum Cystatin C within 24 hours after admission appears to be a good biomarker for predicting of AKI in patients with CAP.

**Abbreviations**

AKI: Acute kidney injury; CAP: Community acquired pneumonia; SCr: Serum creatinine; KDIGO: Kidney Disease Improving Global Outcomes; COPD: Chronic obstructive pulmonary disease; CURB-65: confusion, uremia, respiratory rate, blood pressure, and age 65 years or older; ROC: Receiver operating characteristic; AUC: Area under the receiver operating characteristic curve; ICU: Intensive care unit; NT-proBNP: N-terminal prohormone B-type natriuretic peptide; MR-proANP: mid-regional pro-atrial natriuretic peptide; BNP: B-type natriuretic peptide; PSI: Pneumonia severity index; OR: Odds ratio; CI: Confidence interval; PPV: positive predictive value; NPV: negative predictive value.

**Declarations**

**Ethics approval and consent to participate**

This retrospective study was approved by the Nanjing First Hospital Institutional Review Board and patients’ informed consent was waived due to the retrospective nature of the study.

**Consent for publication**

Not applicable.

**Availability of data and materials**

Data are available on reasonable request. Data are available on reasonable request to the first author (Dawei Chen).

**Competing interests**

The authors declare that they have no competing interests.

**Funding**

This study was supported by grants from Xinghuo Talent Program of Nanjing First Hospital Nanjing Health Science and Technology Development Special Fund Project (Grant No. YKK21129) and The Six-one Project of Top Talents in Jiangsu Province (Grant No. LGY2020014).

**Authors’ contributions**

D-WC, L-LJ and X-W conceived the study and planned and conducted it. M-Q M, W-J H, Y-T, B-BP, and X-BJ acquired the data and performed the data analysis. All authors interpreted the data and wrote the manuscript.
Acknowledgements

Not applicable.

Author details

1 Department of Nephrology, Nanjing First Hospital, Nanjing Medical University, Nanjing, Jiangsu, China; 2 Department of Nephrology, Sir Run Run Hospital, Nanjing Medical University, Nanjing, Jiangsu, China; 3 Department of Respiratory Medicine, Nanjing First Hospital, Nanjing Medical University, Nanjing, Jiangsu, China.

References

1. Aliberti S, Dela Cruz CS, Amati F, Sotgiu G, Restrepo MI. Community-acquired pneumonia. Lancet (London, England). 2021;398:906-19.
2. Akram AR, Singanayagam A, Choudhury G, Mandal P, Chalmers JD, Hill AT. Incidence and prognostic implications of acute kidney injury on admission in patients with community-acquired pneumonia. Chest. 2010;138:825-32.
3. Murugan R, Karajala-Subramanyam V, Lee M, Yende S, Kong L, Carter M, et al. Acute kidney injury in non-severe pneumonia is associated with an increased immune response and lower survival. Kidney Int. 2010;77:527-35.
4. Murugan R, Weissfeld L, Yende S, Singbartl K, Angus DC, Kellum JA. Association of statin use with risk and outcome of acute kidney injury in community-acquired pneumonia. Clin J Am Soc Nephrol. 2012;7:895-905.
5. Chen D, Yuan H, Cao C, Liu Z, Jiang L, Tan Y, et al. Impact of acute kidney injury on in-hospital outcomes in Chinese patients with community acquired pneumonia. BMC Pulm Med. 2021;21:143.
6. Chawla LS, Amdur RL, Faselis C, Li P, Kimmel PL, Palant CE. Impact of Acute Kidney Injury in Patients Hospitalized With Pneumonia. Crit Care Med. 2017;45:600-6.
7. Zhang Z, Lu B, Sheng X, Jin N. Cystatin C in prediction of acute kidney injury: a systemic review and meta-analysis. Am J Kidney Dis. 2011;58:356-65.
8. Kališnik JM, Hrovat E, Hrastovec A, Žibert J, Jerin A, Skitek M, et al. Creatinine, Neutrophil Gelatinase-Associated Lipocalin, and Cystatin C in Determining Acute Kidney Injury After Heart Operations Using Cardiopulmonary Bypass. Artif Organs. 2017;41:481-9.
9. Luo Q, Ning P, Zheng Y, Shang Y, Zhou B, Gao Z. Serum suPAR and syndecan-4 levels predict severity of community-acquired pneumonia: a prospective, multi-centre study. Crit Care. 2018;22:15.
10. Niederman MS, Mandell LA, Anzueto A, Bass JB, Broughton WA, Campbell GD, et al. Guidelines for the management of adults with community-acquired pneumonia. Diagnosis, assessment of severity, antimicrobial therapy, and prevention. Am J Respir Crit Care Med. 2001;163:1730-54.
11. Kellum JA, Lameire N. Diagnosis, evaluation, and management of acute kidney injury: a KDIGO summary (Part 1). Crit Care.2013;17:204.
12. Roussos C, Koutsoukou A. Respiratory failure. Eur Respir J Suppl.2003;47:3s-14s.
13. Lim WS, van der Eerden MM, Laing R, Boersma WG, Karalus N, Town GI, et al. Defining community acquired pneumonia severity on presentation to hospital: an international derivation and validation study. Thorax.2003;58:377-82.
14. Guo J, Zheng C, Xiao Q, Gong S, Zhao Q, Wang L, et al. Impact of anaemia on lung function and exercise capacity in patients with stable severe chronic obstructive pulmonary disease. BMJ open.2015;5:e008295.
15. Wang RR, He M, Gui X, Kang Y. A nomogram based on serum cystatin C for predicting acute kidney injury in patients with traumatic brain injury. Ren Fail.2021;43:206-15.
16. Yang H, Lin C, Zhuang C, Chen J, Jia Y, Shi H, et al. Serum Cystatin C as a predictor of acute kidney injury in neonates: a meta-analysis. J Pediatr (Rio J).2021;S0021-7557(21)00135-2.
17. Heise D, Rentsch K, Braeuer A, Friedrich M, Quintel M. Comparison of urinary neutrophil glucosaminidase-associated lipocalin, cystatin C, and α1-microglobulin for early detection of acute renal injury after cardiac surgery. Eur J Cardiothorac Surg.2011;39:38-43.
18. Chung MY, Jun DW, Sung SA. Diagnostic value of cystatin C for predicting acute kidney injury in patients with liver cirrhosis. Korean J Hepatol. 2010;16:301-7.
19. Barrett AJ, Davies ME, Grubb A. The place of human gamma-trace (cystatin C) amongst the cysteine proteinase inhibitors. Biochem Biophys Res Commun.1984;120:631-6.
20. Grubb AO. Cystatin C–properties and use as diagnostic marker. Adv Clin Chem.2000;35:63-99.
21. Kaseda R, Iino N, Hosojima M, Takeda T, Hosaka K, Kobayashi A, et al. Megalin-mediated endocytosis of cystatin C in proximal tubule cells. Biochem Biophys Res Commun.2007;357:1130-4.
22. Yildirim C, Ozger HS, Yasar E, Tombul N, Gulbahar O, Yildiz M, et al. Early predictors of acute kidney injury in COVID-19 patients. Nephrology (Carlton).2021;26:513-21.
23. Nowak A, Breidthardt T, Dejing S, Christ-Crain M, Bingisser R, Drexler B, et al. Natriuretic peptides for early prediction of acute kidney injury in community-acquired pneumonia. Clin Chim Acta.2013;419:67-72.
24. Fine MJ, Auble TE, Yealy DM, Hanusa BH, Weissfeld LA, Singer DE, et al. A prediction rule to identify low-risk patients with community-acquired pneumonia. N Engl J Med.1997;336:243-50.
25. Wiedermann CJ, Wiedermann W, Joannidis M. Hypoalbuminemia and acute kidney injury: a meta-analysis of observational clinical studies. Intensive Care Med.2010;36:1657-65.
26. Wang F, Ran L, Qian C, Hua J, Luo Z, Ding M, et al. Epidemiology and Outcomes of Acute Kidney Injury in COVID-19 Patients with Acute Respiratory Distress Syndrome: A Multicenter Retrospective Study. Blood Purif.2021;50:499-505.
27. Iglesias J, Abernethy VE, Wang Z, Lieberthal W, Koh JS, Levine JS. Albumin is a major serum survival factor for renal tubular cells and macrophages through scavenging of ROS. Am J
28. Kaufmann MA, Castelli I, Pargger H, Drop LJ. Nitric oxide dose-response study in the isolated perfused rat kidney after inhibition of endothelium-derived relaxing factor synthesis: the role of serum albumin. J Pharmacol Exp Ther. 1995;273:855-62.

29. Dubois MJ, Orellana-Jimenez C, Melot C, De Backer D, Berre J, Leeman M, et al. Albumin administration improves organ function in critically ill hypoalbuminemic patients: A prospective, randomized, controlled, pilot study. Crit Care Med. 2006;34:2536-40.

30. Lee EH, Kim WJ, Kim JY, Chin JH, Choi DK, Sim JY, et al. Effect of Exogenous Albumin on the Incidence of Postoperative Acute Kidney Injury in Patients Undergoing Off-pump Coronary Artery Bypass Surgery with a Preoperative Albumin Level of Less Than 4.0 g/dl. Anesthesiology. 2016;124:1001-11.

31. Xu X, Hu J, Song N, Chen R, Zhang T, Ding X. Hyperuricemia increases the risk of acute kidney injury: a systematic review and meta-analysis. BMC nephrology. 2017;18:27.

32. He L, Zhang Q, Li Z, Shen L, Zhang J, Wang P, et al. Incorporation of Urinary Neutrophil Gelatinase-Associated Lipocalin and Computed Tomography Quantification to Predict Acute Kidney Injury and In-Hospital Death in COVID-19 Patients. Kidney Dis (Basel). 2021;7:120-30.

33. Wu M, Luan YY, Lu JF, Li H, Zhan HC, Chen YH, et al. Platelet count as a new biomarker for acute kidney injury induced by hemorrhagic shock. Platelets. 2020;31:94-102.

34. Kertai MD, Zhou S, Karhausen JA, Cooter M, Jooste E, Li YJ, et al. Platelet Counts, Acute Kidney Injury, and Mortality after Coronary Artery Bypass Grafting Surgery. Anesthesiology. 2016;124:339-52.

35. Yang J, Zhou J, Wang X, Wang S, Tang Y, Yang L. Risk factors for severe acute kidney injury among patients with rhabdomyolysis. BMC nephrology. 2020;21:498.

36. Patidar KR, Xu C, Shamseddeen H, Cheng YW, Ghabril MS, Mukthinuthalapati V, et al. Development and Validation of a Model to Predict Acute Kidney Injury in Hospitalized Patients With Cirrhosis. Clin Transl Gastroenterol. 2019;10:e00075.

Figures
5851 hospitalized patients diagnosed with CAP

2338 patients without Cystatin C

3513 hospitalized patients diagnosed with CAP

797 patients excluded:
(1) 406 patients with less than two repeated serum creatinine.
(2) 28 patients with a history of end stage renal disease or requiring dialysis.
(3) 363 patients lacking complete medical records.

2716 hospitalized patients diagnosed with CAP

1950 (72%) patients without AKI

766 (28%) patients with AKI

Figure 1

Flowchart for patient selection.

Abbreviations: CAP: community acquired pneumonia; AKI: acute kidney injury.
Figure 2

Comparisons of AUCs for all independent factors of AKI in patients with CAP.

Abbreviations: AUC: area under the receiver operating characteristic curve; CAP: community acquired pneumonia; AKI: acute kidney injury; CURB-65: confusion, uremia, respiratory rate, blood pressure, and age 65 years or older.
Figure 3

Prediction efficiency of serum Cystatin C for AKI in various subgroups of patients with CAP.

Abbreviations: AKI: acute kidney injury; CAP: community acquired pneumonia; CI: Confidence interval; AUC: Area under the receiver operating characteristic curve; COPD: Chronic obstructive pulmonary
disease; CURB-65: confusion, uremia, respiratory rate, blood pressure, and age 65 years or older; ROC: Receiver operating characteristic; ICU: Intensive care unit.