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### Patient-centered approach to the management of acute kidney injury in the Covid-19 outcomes

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#### ABSTRACT

Aim: To identify patients at risk of AKI with severe COVID-19 and to guide management strategies according to national and global scientific data for improving kidney-related outcomes.

Materials and Methods: We conducted retrospective study case-control analysing cases of hospitalisation patients with COVID-19 with or without AKI during hospital stay.

**Results:** In the study, we found that there was a positive correlation between AKI and respiratory insufficiency (0,513 - moderate, p<0,0001), moderate in the case of AKI grade 2 (0.301, <0,001) and mild in the case of AKI grade 1 and 3 correspondingly (0.252, p<0,01; 0.277, <0,001). Lethality (in-hospital death rate) correlated with respiratory insufficiency and AKI (0.733, 0,617; p<0,0001). We found that age had a reverse correlation with AKI and RI (younger patients were more likely to have a higher prevalence of AKI and RI, p<0,001). It was noticed that AKI correlated with the minimal albumin level (-0,35, p=0,016), minimal lymphocyte count (-0.377, p<0,0001), IL-6 (0.201, p=0,035), ferritin (0.34, p<0,0001), maximal CRP (0.439, p<0,0001). There was a mild correlation between Padua Score and AKI (0,232, p<0,01) and PLRI (0,172, p=0,05).

**Conclusions:** Early assessment of renal dysfunction could be used as a marker of severe outcomes of COVID-19, especially in the case of comorbidities such as metabolic disorders and cardiovascular events. We suggest using the Padua score, assessment of personal lethality risk index (PLRI), and rise of serum creatinine as additional tools for assessment criteria for hospitalisation.

KEY WORDS: COVID-19, prevention, acute kidney injury, public health, treatment

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#### INTRODUCTION

Community-acquired COVID-related acute kidney injury (AKI) is an important research direction. We tried to find approaches to optimise health care, focusing on diagnosing and managing AKI. The interrelationships between respiratory insufficiency, sepsis and AKI should still be discussed. According to the Kidney Disease Improving Global Outcomes (KDIGO) consensus, AKI is defined as a sudden loss of excretory kidney function [1], with the onset of development within seven days. AKI affects about half of patients admitted to the intensive care unit (ICU) and worsens their short- and long-term outcomes [2, 3]. AKI has a high prevalence in patients with COVID-19 hospitalised in the ICU [4]. Combining serum creatinine (SCr) and cystatin C provided good risk prediction in AKI [5, 6].

#### AIM

The study aims to identify patients at risk of AKI with severe COVID-19 and to guide management strategies

according to national and global scientific data for improving kidney-related outcomes.

#### MATERIALS AND METHODS

The research methods included medical and statistical, content analysis, structural-logical analysis, clinical, laboratory, and instrumental techniques. We conducted retrospective study case-control analysing cases of hospitalisation patients with COVID-19 with or without AKI during hospital stay.

#### RESULTS

We conducted retrospective analysis of hospitalisation due to COVID-19 with or without AKI in the group of patients hospitalised to private hospital in Kyiv (n=129) (Table 1). The group was divided into 2 groups: those who had AKI and those who did not have significant changes in kidney function. We performed statistical analysis of data using

#### AKI group (n=19) Non-AKI group (n=110) р Males 10, females 9 Males 46, females 64 Males, 52,6 (29,2-75,5) 41,8 (32,7-51,2) p=0,536. % BMI, 30.6±2.3 28.42±1.2 p=0,473. kg/m2 Age, years 79 (64-80) 81 (78-84) p<0,001 (Me, IQR) LYM\*109/I 0,2 (0,1-0,39) 0,5 (0,34-0,76) (n=109) p<0,001. (Me, IQR) Maximum grade of respiratory insufficiency, 3 (3-3) 1 (1-2) p<0,001 (Me, IQR) Duration of hospital stay 14 (9-22) 10 (7-13) p=0,025 (Me, IQR) % CT 61 (40-75) 30 (15-50) p=0,004. (Me, IQR) N=85 N=14 CRP, mg/l 134,26 (93.54-185.06) 44,765 (20.43-93.26) p<0,001. (Me, IQR) N=19 N=110 HbA1c.% 5.5 (5.09-7.07) 5.29 (4.79-5.95) p=0,111. (Me, IQR) N=18 N=106 Ferritin, mcg/l 1094 (686-1176) 375 (187-647.5) p<0,001. (Me, IQR) N=17 N=107 IL-6 pg/mL, Me 48,55 (18-110,65) 25,1 (10,2-46,2) p=0,029. (Me, IQR) N=16 N=97 Baseline eGFR (on admission), ml/min\*1,73 60.41±5.61 60,06±1,96 p=0,944. CKD, N=19 N=106 Minimal eGFR, ml/min\*1,73 18,4 (10,7-27,4) 58,55 (42,1-74,9) p<0,001. (Me, IQR) N=19 N=94 Min eGFR, ml/min\*1,73 19,78±2,42 (p<0,001.) p<0,001. M±m ALT, U/L, 29.1 (22,9-37,6) 26.9 (16.9-41) p=0,339. Me (QI-QIII) N=19 N=108 AST, U/L, 36.9 (26.8-67.9) 35.4 (25.7-46.65) p=0,258. Me (QI-QIII) N=108 N=19 AST/ ALT, 1,38 (1.11-1.47) 1,31 (1-1.77) p=0,850. Me (QI-QIII) N=19 N=108 Baseline Albumin (on admission), g/L, Me (QI-QIII) 32.07 (31.1-36.3) 33.68 (31.53-35.8) p=0,588. Albumin (on admission), g/L, M±m 33.37±1.1 Minimal Albumin, g/L, M±m 27,64±0.9 (p<0,001.) 32.02 (26.37-35.91) (p<0,001.) Prevalence of Diabetes Mellitus, % (95% CI) 26,3 (8,6-49,4) 24 (16,1-32.9) p=0,936. Prevalence of cough, % (95% CI) 31.6 (12,1-55,2) 49.1 (39.7-58.5) p=0,240. Prevalence of Dyspnea, % (95% CI) 47.4 (24,5-70.8) 36.4 (27.6-45.6) p=0,517. Prevalence of fever, % (95% CI) 68,4 (44.8-87.9) 76.4 (67,9-83.9) p=0,661. Prevalence of frailty, % (95% CI) 94.7 (79.3-100) 96.4 (92-99.1) p=0,742. Prevalence of diarrhea, % (95% CI) 10.5 (0,8-29,2) 8,2 (3,8-14,1) p =0,913. Lethality (in both groups 31.8 (24-40.1) 100 (90.5-100) 20 (13-28) p<0,001. COMORBIDITY\*[9] 2 (1-3) 2 (1-3) p=0,547. PLRI (personalized lethality risk index)[9] 5.1±0.4 4.3±0.2 p=0,048. 3 (3-3) Padua Score 4 (3-4) p=0,010. Increase in SCr, times (95% CI) 2.25 (1.77-4.37) 1 (1-1.04) p<0,001. Prevalence of Grade 1 AKI, % (95% CI) 26,3 (8.6-49.4) Prevalence of Grade 2 AKI, % (95% CI) 36,8 (16-60,7) Prevalence of Grade 3 AKI, % (95% CI) 36,8 (16-60,7)

#### Table 1. Clinical and laboratory findings in hospitalised COVID- inpatients in the groups (with AKI and without AKI)

| AKI & RI       | 0.513  |         | AKI & RI        |        |         |
|----------------|--------|---------|-----------------|--------|---------|
|                |        |         | GRADE1          | 0.252  | <0,01   |
|                |        |         | GRADE2          | 0.301  | <0,001  |
|                |        |         | GRADE3          | 0.277  | <0,001  |
| RI & Lethality | 0.733  | <0,0001 | AKI & Lethality | 0.617  | <0,0001 |
| RI & AGE       | -0.375 | <0,0001 | AKI & AGE       | -0.304 | <0,001  |
| RI & ALB min   | -0.532 | <0.001  | AKI & ALB min   | -0.35  | 0,016   |
| RI & PADUA     | 0.426  | <0,0001 | AKI & PADUA     | 0.232  | <0,01   |
| RI & IL-6      | 0.388  | <0,0001 | AKI & IL-6      | 0.201  | 0,035   |
| RI & CRP max   | 0.467  | <0,0001 | AKI & CRP max   | 0.439  | <0,0001 |
| RI & FERR      | 0.451  | <0,0001 | AKI & FERR      | 0.34   | <0,0001 |
| RI & LYM       | -0.611 | <0,0001 | AKI & LYM       | -0.377 | <0,0001 |
| RI & Duration  | 0.376  | <0,0001 | AKI & Duration  | 0.206  | 0,02    |
| RI & PLRI      | 0.406  | <0,0001 | AKI & I PLRI    | 0.172  | 0,05    |

Table 2. Rank correlation indexes between AKI and respiratory insufficiency (RI) -associated conditions

Medstat. When performing the analysis for quantitative indicators, the mean value (M), standard error (±m) and 95% confidence interval (95% CI) were calculated for the normal distribution, and the median value (Me) and interquartile range (QI–QIII) were calculated for the non-normal distribution. For qualitative indicators, prevalence (%) and 95% confidence interval (95% CI) were calculated. The Mann-Whitney test was used to compare mean values in two groups for quantitative measures, and the chi-square test (with Yates' correction) was used to compare qualitative measures. All calculations were performed for a critical significance level of 0.05.

We used AKI criteria based on KDIGO (Kidney Disease Improving Global Outcomes) criteria in patients with elevated baseline serum creatinine (SCr); stage 1—increase in SCr by 0.3 mg/dl within 48 hours or a 1.5 to 1.9 times increase in SCr from baseline within seven days; stage 2—2.9 times increase in serum creatinine within seven days; stage 3—3 times or more increase in SCr within seven days or the initiation of RRT [1, 8].

In our previous study we proposed using personalized lethality risk index (PLRI) calculation as an indicator summarising the following criteria, such as presence of comorbidities (arithmetic sum of the number of organ systems affected by a chronic pathology according to ICD-10, or COMORB); 2) age over 70 years; 3) presence of obesity (BMI more than 30 kg/m2); 4) presence of cardiovascular disease; 5) neurological pathology (cerebrovascular events) in the past; 6) respiratory failure with decreased blood saturation (SpO2 < 92 %), requiring the oxygen therapy and glucocorticoid administration; 7) pulmonary parenchymal involvement over than 50 %.The presence of one of the above criteria resulted in a score of 1. The personalized lethality risk index was calculated as the sum of these scores [9]. We also calculated rank correlation indexes between AKI and respiratory insufficiency (RI) -associated conditions and presented them in the table 2.

In our study, we found that there was a positive correlation between AKI and respiratory insufficiency (0,513 - moderate, p<0,0001), moderate in the case of AKI grade 2 (0.301, <0,001) and mild in the case of AKI grade 1 and 3 correspondingly (0.252, p<0,01; 0.277, <0,001). Lethality (in-hospital death rate) correlated with respiratory insufficiency and AKI (0.733, 0,617; p<0,0001). We found that age had a reverse correlation with AKI and RI (younger patients were more likely to have a higher prevalence of AKI and RI, p<0,001). It was noticed that AKI correlated with the minimal albumin level (-0,35, p=0,016), minimal lymphocyte count (-0.377, p<0,0001), IL-6 (0.201, p=0,035), ferritin (0.34, p <0,0001), maximal CRP (0.439, p<0,0001). There was a mild correlation between Padua Score and AKI (0,232, p<0,01) and PLRI (0,172, p=0,05).

#### DISCUSSION

The pathophysiology of COVID-19-associated AKI could be due to multiple mechanisms such as direct viral kidney injury, immune-induces autoimmune reactions or hyperinflammation, sepsis, non-specific pre-renal mechanism, nephrotoxicity of some medications or mechanical ventilation, hypoxemia [3,7, 9, 10].

The pathophysiology of COVID-19-associated AKI could be related to non-specific mechanisms but also to COVID-induced mechanisms, such as direct injury resulting from viral entry through the receptor angiotensin-converting enzyme 2 (ACE2), which is highly expressed in the kidney, an imbalanced renin-angiotensin-aldosterone system, pro-inflammatory cytokines

elicited by the viral infection and thrombotic events, as well it could be caused by non-specific mechanisms include hemodynamic alterations, right heart failure, high levels of PEEP in patients requiring mechanical ventilation, hypovolemia, administration of nephrotoxic drugs, and nosocomial sepsis [12]. Local inflammation and hyperinflammatory immune response could be considered a key role in AKI, as endothelial injury and microvascular clots are essential in the pathophysiology of AKI. However, the issue of renal tropism remains controversial [12].

AKI could be observed in the structure of multiple organ damage in severe and critically ill COVID-19 patients. As it illustrates the influence of cytokine storm on organ lesions, AKI is also caused by hypoxemia [13]. Hirsch J. S. et al., 2020 reported that among patients who required mechanical ventilation, 89.7% had AKI compared with 21.7% in nonventilated patients [14].

Ng J.H. et al., 2020, reported that among 9,657 patients admitted with COVID-19 to the 13 hospitals in New York in 2020, the AKI incidence rate was 38.4/1,000 patient-days and incidence rates of in-hospital death among patients without AKI, with AKI not requiring dialysis (AKI stages 1-3), and with AKI receiving dialysis (AKI 3D) were 10.8, 31.1, and 37.5/1,000 patient-days, respectively [11].

Menez S. et al., 2023 reported that an increase in soluble tumour necrosis factor receptor 1 (sTNFR1) and sTNFR2 was significantly associated with an increased risk of major adverse kidney events (MAKE) [15]. Noticeably, kidney dysfunction is considered to be quite frequent as mild proteinuria or any other urine abnormalities in urinalysis may be often observed in non-severe cases. Still, as well it could predict AKI that causes urgent dialysis necessity or other renal replacement therapy (RRT) [13]. The cost of hospital stay and duration of treatment increases while AKI happens [14, 16, 17]. Wainstein M. et al. (2023) suggest analysing AKI in the severity of the disease (on the individual level) and in the global context, comparing the international effectiveness of health systems while analysing results from countries with different income levels. The authors divided countries by income level and compared AKI incidence during hospital stays [16]. The critical question is whether prevention of AKI is possible and how it could be prevented. However, the answer could be challenging as the necessity of hospitalisation was considered differently in different countries and varied greatly, depending on the health system and medical facilities.

Understanding the mechanisms of kidney damage and AKI in the setting of critical illness and COVID-19 is important, and it can provide a possibility for improvement in health care [14, 17]. The main methods of RRT include dialysis and renal transplantation, but globally, it is thought to be challenging due to numerous economic, social, and other factors [18]. Hemodialysis and peritoneal dialysis are equally efficient, and it is essential to raise the awareness of patients and the level of medical staff education and provide equal access to all renal replacement therapy types worldwide [18]. During a pandemic or martial period in Ukraine, while the resources are limited and the massive hospitalization with the necessity of urgent RRT could be observed, acute kidney injury developing on the battlefield, in field hospitals or higher-level hospital settings is characterized by poor outcomes [19]. It was reported that patients with AKI and COVID-19 more often required RRT and less frewuently recovered kidney function [20].

Neirynck N. et al., 2015 concluded that both sTNFR1 and sTNFR2 could help predict the outcome of chronic kidney disease (CKD), including diabetic nephropathy, associated with increased all-cause mortality or an increased risk for cardiovascular events (CVE) in advanced CKD irrespective of the cause of kidney disease [21].

To prevent poor outcomes of COVID-19, we propose analysing clinical and laboratory findings. Suppose the person has chronic non-communicable diseases, such as CVD, arterial hypertension, diabetes, metabolic disorders, psychiatric or neurological pathology, especially with high initial ferritin, C-reactive protein, IL-6 levels or poor dynamics. In that case, it is advisable to hospitalise the person after assessing the individual risks. Further study is necessary to clarify the possibility of personal assessment and risk calculation tools based on evidence-based medicine. However, high mortality could be explained by late admission or rapid organ failure in the case of secondary hemophagocytic lymphohistiocytosis. It is necessary to use pandemic experience in the future. Early renal replacement therapy is essential for the effectiveness of AKI grade 3 management to prevent severe complications and in-hospital deaths.

#### CONCLUSIONS

It was noticed that AKI correlated with the minimal albumin level (-0,35, p=0,016), minimal lymphocyte count (-0.377, p<0,0001), IL-6 (0.201, p=0,035), ferritine (0.34, p<0,0001), maximal CRP (0.439, p<0,0001). There was a mild correlation between Padua Score and AKI (0,232, p<0,01) and PLRI (0,172, p=0,05). Early assessment of renal dysfunction could be used as a marker of severe outcomes of COVID-19, especially in the case of comorbidities such as metabolic disorders and cardiovascular events. We suggest using the Padua score, assessment of PLRI, and rise of serum creatinine as additional tools for assessment criteria for hospitalisation.

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#### **CONFLICT OF INTEREST**

The Author declare no conflict of interest

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