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## Original Article



## Case Report



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# ESTIMATES OF GLOMERULAR FILTRATION RATE BASED ON CREATININE, CYSTATIN C AND COMBINATION OF CREATININE AND CYSTATIN C EQUATIONS IN CRITICALLY ILL PATIENTS

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## ABSTRACT

*Introduction:* Accurate assessment of renal function in the critically ill is important for the diagnostic and prognostic utility to guide clinical management. It is usually estimated from various estimate glomerular filtration rate (eGFR) equations. We evaluated eGFR based on Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation using serum creatinine (Cr), Cystatin C (CysC), and its combination, against 24-hour creatinine clearance (CrCl). We aimed to find the most accurate, precise, and less biased equation for GFR estimation.

*Methods:* Critically ill patients, older than 18 years who stayed longer than 24 hours were included in the study. Urinary creatinine, serum Cr, and CysC were measured at three-time points (8, 24, and 72 hours). We then compared eGFR from Cr ($eGFR_{Cr}$), CysC ($eGFR_{CysC}$) and combined CKD-EPI ($eGFR_{Cr\text{-}CysC}$) to the measured 24-hour CrCl.

*Results:* A total of 43 patients were recruited. $eGFR_{Cr}$ had the highest correlation to CrCl, with correlation of 0.81 and 0.73 at 24 and 72 hours, respectively, and was the most precise and accurate equation compared to $eGFR_{CysC}$ and $eGFR_{Cr\text{-}CysC}$ at all-time points. The bias was lowest for $eGFR_{CysC}$ equation. The Area Under Curve of $eGFR_{Cr}$ in diagnosing acute kidney injury (AKI) was 0.93 and 0.84 at 24 and 72 hours, respectively. Neither the eGFR equations nor CrCl played a role in the prediction of in-hospital mortality.

*Conclusion:* $eGFR_{Cr}$ had the highest correlation to CrCl and was the most accurate and precise equation, however, $eGFR_{CysC}$ had lowest bias. Most of the equations contributed to the diagnosis of AKI. However, none on contributed to the prediction of in-hospital mortality.

***Keywords:*** *Estimated Glomerular Filtration Rate, Serum Creatinine, Serum Cystatin C, Intensive Care Unit.*

## INTRODUCTION

Accurate assessment of kidney function in critically ill patients is important for correct drug dosing, fluid requirement, adequacy of nutrition, and early detection of kidney injury (AKI) (1,2). A standard measure for renal function calculation is estimates of glomerular filtration rate (eGFR) (3). Measurement of glomerular filtration rate (GFR) can be performed either by the clearance of exogenous filtration markers such as inulin or by the clearance of endogenous filtration markers such as serum creatinine (Cr), or serum Cystatin C (CysC) (4,5). However, these are not usually used in daily practice and research due to challenges in sample assortment, expense, inconvenience, and time consumption (8,9,10). More common in the clinical setting is the measurement using 24-hour creatinine clearance (CrCl) (9). However, the challenges for 24-hour CrCl include difficulty of a scheduled urine collection and failure in obtaining a

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perfect specimen (10).

Estimation of GFR is usually focused on endogenic compounds, as it is more accessible and convenient (11). Various eGFR equations are available since the first equation introduced in 1957(9,12). However, most were developed in non-critically ill populations. Serum Cr is insensitive to rapidly changing GFR, and is influenced by age, sex, muscle mass, diet, and tubular secretion of creatinine (13,14,15). CysC is a 13kDA molecule which is freely filtered from glomerulus and is catabolised from the proximal renal tubule (16). CysC is not influenced by muscle mass and dietary protein intake, hence is a better filtration marker than Cr (17).

Equations based on CysC have been introduced for diagnosis of kidney disease because of its independence from many factors that affect Cr. (7). However, in ICU patients the actual advantage of CysC over Cr equations in estimating true GFR still remains unclear (18,19) eGFR estimates from the combination of Cr and CysC have been shown to be more advantageous than eGFR based on either marker alone (20). The National Kidney Foundation Disease Outcomes Quality Initiative (KDOQI) recommended the use of estimates of GFR calculated from predicting equations based on Cr, CysC and their combination (4). To date, there are few studies investigating Cr and CysC based equation for estimating GFR in critical care patients. We aimed to evaluate which of these equations performed best in our critically ill patients, and if there is any difference in patients with AKI and those without AKI.

## MATERIALS AND METHOD

This is a single center, cross-sectional observational study in critically ill patients of Sultan Ahmad Shah Medical Centre, Islamic University of Malaysia (SASMEC@ IIUM). This study has been approved by IIUM Research Ethical Committee (IREC Number 2019-185). Consent was obtained from the patient or legally-approved representative. All critically ill patients older than 18 years, who stayed in the ICU for more than 24 hours with a urinary catheter in place were included in the study. Patients on diuretics, dialysis, with thyroid dysfunction, post elective surgery, and pregnant females were excluded from the study. In addition, anuric patients were excluded due to lack of urine collection for CrCl measurement.

Blood samples were centrifuged at 3600 rpm for 15 minutes and the plasma were stored at -80$^0$C for batch analysis. Serum and urinary creatinine measured at 8, 24 and 72 hours, were assayed using Modified JAFFA method Chemistry Analyzer (Cobas Integra 400 plus, Roche, Indianapolis, USA). Serum CysC, measured at 12 and 24 hours were assayed using Fine Care CysC Rapid Test (Wondfo Biotech). Urine was collected over 24 hours on day 1 and day 3, and the total volume collected was recorded. Urinary creatinine and plasma creatinine were measured at these time points. From these, 24-hour CrCl were calculated for day 1 and day 3. GFR was estimated based on the Chronic Kidney Disease Epidemiologic Collaboration (CKD-EPI) equations based on Cr ($eGFR_{Cr}$), CysC ($eGFR_{CysC}$), and their combination ($eGFR_{Cr\text{-}CysC}$)

Other data collected include age, sex, height, weight, ethnicity, medical or surgical admission, primary admission diagnosis, co-morbidities, length of ICU and hospital stay, and mortality. The baseline Acute Physiology and Chronic Health Evaluation (APACHE) II and Sequential Organ Failure Assessment (SOFA) scores were used to assess severity of illness in each patient. AKI was defined based on baseline creatinine value at the time of admission based on the Kidney Disease Improving Global Outcome (KDIGO) guideline. Patients were followed-up until discharged from the hospital to determine the outcome parameters studied.

## STATISTICAL ANALYSIS

Statistical analyses were performed using SPSS® Statistics version 25 (IBM, New York, USA for the statistical analysis). Sample size was calculated using MedCalc® Software version 18.11.6. Comparison of variables between two groups were analysed using the independent t-test for normally distributed variables, or the Mann-Whitney U test for non-normally distributed variables. Categorical variables were compared using the Chi-square test. Pearson correlation was used for the analysis of normally distributed variables, and Spearman correlation for non-normally distributed variables. Bland Altman analysis was performed using 95% limits of agreement that were calculated as the mean difference ± 1.96 SD. The mean difference between estimated GFR and measured CrCl was defined as bias, while precision was expressed as the SD of this difference. The proportion of eGFR within 30 percent of the measured CrCl was described as accuracy. The receiver operating characteristic (ROC) curve of the sensitivity verse 1-specificity was used to diagnostic and predictive ability of eGFR equations to assess area under curve (AUC).

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## RESULT

One hundred sixty-two patients were screened between 1st October 2019 to 20th March 2020. Patients less than 18 years (n=6), post elective surgery (n=41), with no consent (n=25), no urine output (n=23), technical problem in urine collection (n=10), ICU admission of less than 24 hours (n=7), and patient with dialysis (n=7) were excluded. Of screened patients, 43 were enrolled in the study. Of this 26 stayed for more than 72 hours, and 13.9% died in the hospital (Figure 1). All patients recruited have a complete 24-hour urine collection for CrCl measurement on day 1. However, CrCl measurements were not available in 17 (39.5%) of patients in day 3 as they were already discharged from the ICU.

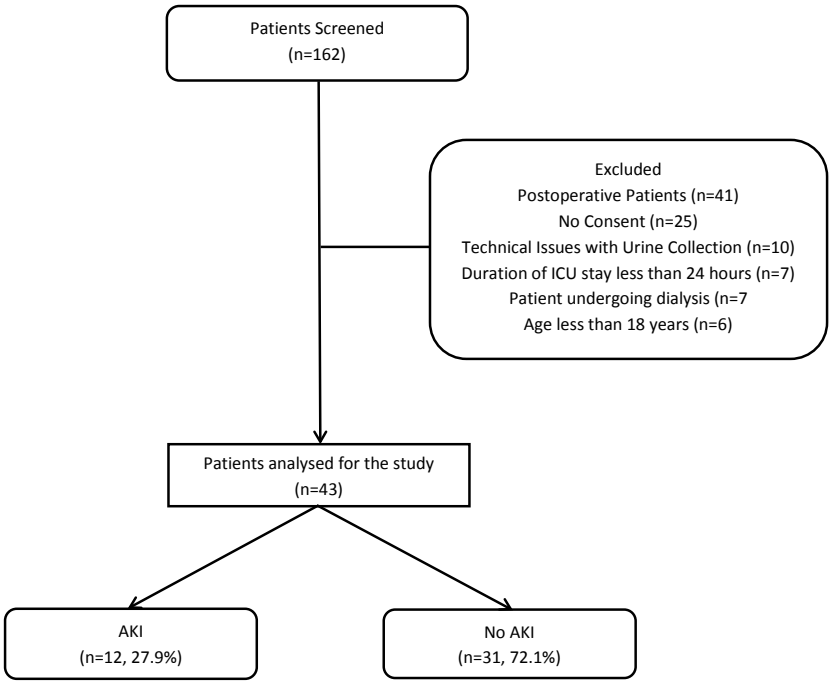


*Figure 1: Plain chest radiograph showing bilateral heterogenous patchy opacities*

### *Demographic, Clinical Characteristics and Outcomes*

TTable I compares the baseline demographic, clinical characteristics and outcome for patients with AKI and without AKI. Of the 43 patients recruited, 26 (60.4%) patients stayed in the ICU for more than 3 days. The median length of ICU stay was 6 days (IQR 3 days). Majority of our study patients was of medical category (88.3%), with infective disease (34.9 %) and respiratory disease (27.9%) as the leading causes of admission. Patients with AKI were older and had higher APACHE II and SOFA scores on ICU admission compared to those without AKI. There were no differences in other parameters. Six patients (13.9%) died during the hospital admission, and there were no differences in AKI and No AKI group. There were no differences in age, and severity score of SOFA and APACHE II in survivor and non-survivor.

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*Table I: Demographic, clinical characteristics, and patient outcome*

| Variables | All patients n=43 | AKI n=12 | No-AKI. n=31 | P-value |
|---|---|---|---|---|
| Age (years) | 61.0 (17.0) | 68.0 (14.0) | 59.0 (18.0) | 0.041 |
| Ethnicity | | | | |
| • Malay | 38.0 (88.4) | 11.0 (91.7) | 27.0 (87.1) | 0.644 |
| • Indian | 3.0 (7.4) | 0.0 (0.0) | 2.0 (6.5) | |
| • Chinese | 2.0 (4.2) | 1.0 (8.3) | 2.0 (6.5) | |
| Gender (male) | 27.0 (62.7) | 9.0 (75.0) | 18.0 (58.1) | 0.308 |
| Height (m) | 162.0 (14.0) | 162.0 (11.0) | 163.0 (14.0) | 0.989 |
| Weight (kg) | 70.0 (26.0) | 75.0 (29.0) | 70.0 (30.0) | 0.221 |
| Sepsis | 39.0 (91.7) | 12.0 (100) | 27.0 (87.1) | 0.197 |
| | | 0.0 (0.0) | 4.0 (12.9) | |
| Admission Category | | | | 0.679 |
| • Medical | 38.0 (88.4) | 11.0 (91.7) | 27.0 (87.1) | |
| • Surgical | 5.0 (11.6) | 1.0 (8.3) | 4.0 (12.9) | |
| SOFA score | | | | |
| • Day 1 | 5.5 (4.0) | 6.0 (5.0) | 3.0 (5.0) | 0.076 |
| • Day 3 | 5.0 (3.0) | 5.0 (3.0) | 4.5 (4.0) | 0.231 |
| APACHE II scores | | | | |
| • Day 1 | 14.0 (6.0) | 17.0 (10.0) | 12.0 (5.0) | 0.018 |
| • Day 3 | 11.0 (5) | 15.0 (10.0) | 11.0 (2.0) | 0.023 |
| Length of Hospital Stay (days) | 11.0 (11.0) | 12.5 (22.0) | 11.0 (10.0) | 0.232 |
| Length of Stay, ICU (days) | 6.0 (9.0) | 5.0 (7.0) | 8.0 (6.0) | 0.254 |
| Discharge status | | | | 0.508 |
| • Alive | 37.0 (86.0) | 11.0 (91.7) | 26.0 (83.9) | |
| • Dead | 6.0 (13.9) | 1.0 (8.3) | 5.0 (16.1) | |
| Primary Diagnoses | | | | 0.732 |
| • Endocrine/Metabolic | 2.0 (4.7) | 0.0 (0.0) | 2.0 (6.5) | |
| • Renal | 5.0 (11.6) | 3.0 (25.0) | 2.0 (6.5) | |
| • Neurological | 3.0 (7.0) | 1.0 (8.3) | 2.0 (6.5) | |
| • Respiratory | 12.0 (27.9) | 3.0 (25.0) | 9.0 (29.0) | |
| • Connective tissue / Auto-immune | 1.0 (2.3) | 0.0 (0.0) | 1.0 (3.2) | |
| • Cardiovascular | 5.0 (11.6) | 1.0 (8.3) | 4.0 (12.9) | |
| • Infective | 15.0 (34.9) | 4.0 (33.3) | 11.0 (35.5) | |
| Baseline co-morbidities | | | | |
| • Myocardial infarction | 6.0 (14.0) | 2 (16.67) | 4 (12.9) | 0.752 |
| • Congestive heart failure | 10.0 (23.3) | 5 (41.6) | 5 (16.1) | 0.079 |
| • Solid tumor | 2.0 (4.7) | 1 (8.3) | 1 (3.2) | 0.118 |
| • Moderate to severe CKD | 9.0 (20.9) | 5 (41.6) | 4 (12.9) | 0.040 |
| • Diabetes Mellitus | 20.0 (44.2) | 3 (25) | 16 (51.6) | 0.420 |
| • Hemiplegia | 3.0 (7.0) | 1 (8.3) | 2 (6.4) | 0.830 |
| • Connective tissue disease | 2.0 (4.7) | 1 (8.3) | 1 (3.2) | 0.481 |
| • Peptic ulcer disease | 2.0 (4.7) | 0 | 2 (6.4) | 0.373 |
| • PVD | 2.0 (4.7) | 1 (8.3) | 1 (3.2) | 0.481 |
| • COPD | 2.0 (4.7) | 1 (8.3) | 1 (3.2) | 0.481 |
| • CVA-TIA | 5.0 (11.6) | 1 (8.3) | 4 (12.9) | 0.679 |

*Data expressed as median (IQR) or n (%), ICU, Intensive Care Unit; SOFA, Sepsis-related Organ Failure Assessment; APACHE, Acute Physiological Assessment and Chronic Health Evaluation; AKI, Acute Kidney Injury; PVD, Peripheral Vascular Disease; COPD, chronic obstructive pulmonary disease; CVA-TIA, Cardiovascular Accident-Transient Ischemic Attack.*

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## Correlation Analyses

All eGFR equations were significantly correlated to the CrCl (Table II). At 24 hours, $eGFR_{Cr}$ had the highest and strong positive correlation to CrCl, with correlation coefficient of 0.810. $eGFR_{CysC}$ had the weakest correlation to CrCl. At 72 hours, $eGFR_{Cr}$ had highest positive correlation compared to other equations with correlation coefficient of 0.733, followed by $eGFR_{Cr\text{-}CysC}$ with correlation coefficient of 0.648.

*Table II: Spearman correlation analysis of CrCL with estimated GFR equations*

| Time<br>All Patients (n=43) | | Variables | Correlation coefficient (r) | *P value* |
|---|---|---|---|---|
| 8 hours | CrCl | $eGFR_{Cr}$ | 0.775 | <0.0001 |
| 24 hours | CrCl | $eGFR_{Cr}$ | 0.810 | <0.0001 |
| | CrCl | $eGFR_{CysC}$ | 0.433 | 0.0004 |
| | CrCl | $eGFR_{Cr\text{-}CysC}$ | 0.651 | <0.0001 |
| 72hrs | CrCl | $eGFR_{Cr}$ | 0.733 | <0.0001 |
| | CrCl | $eGFR_{CysC}$ | 0.510 | 0.0008 |
| | CrCl | $eGFR_{Cr\text{-}CysC}$ | 0.648 | <0.0001 |
| **AKI Patients (n=12)** | | | | |
| 8 hours | CrCl | $eGFR_{Cr}$ | 0.799 | 0.002 |
| 24 hours | CrCl | $eGFR_{Cr}$ | 0.942 | <0.0001 |
| | CrCl | $eGFR_{CysC}$ | 0.296 | 0.351 |
| – | CrCl | $eGFR_{Cr\text{-}CysC}$ | 0.620 | 0.031 |
| 72hrs | CrCl | $eGFR_{Cr}$ | 0.955 | <0.0001 |
| | CrCl | $eGFR_{CysC}$ | 0.562 | 0.091 |
| | CrCl | $eGFR_{Cr\text{-}CysC}$ | 0.812 | 0.004 |
| **No AKI Patients (n=31)** | | | | |
| 8 hours | CrCl | $eGFR_{Cr}$ | 0.545 | 0.002 |
| 24 hours | CrCl | $eGFR_{Cr}$ | 0.492 | 0.005 |
| | CrCl | $eGFR_{CysC}$ | 0.425 | 0.017 |
| | CrCl | $eGFR_{Cr\text{-}CysC}$ | 0.425 | 0.017 |
| 72hrs | CrCl | $eGFR_{Cr}$ | 0.473 | 0.064 |
| | CrCl | $eGFR_{CysC}$ | 0.373 | 0.154 |
| | CrCl | $eGFR_{Cr\text{-}CysC}$ | 0.439 | 0.089 |

*eGFR, estimated glomerular filtration; CrCl, Creatinine clearance; CCr, creatinine; CysC, Cystatin C*

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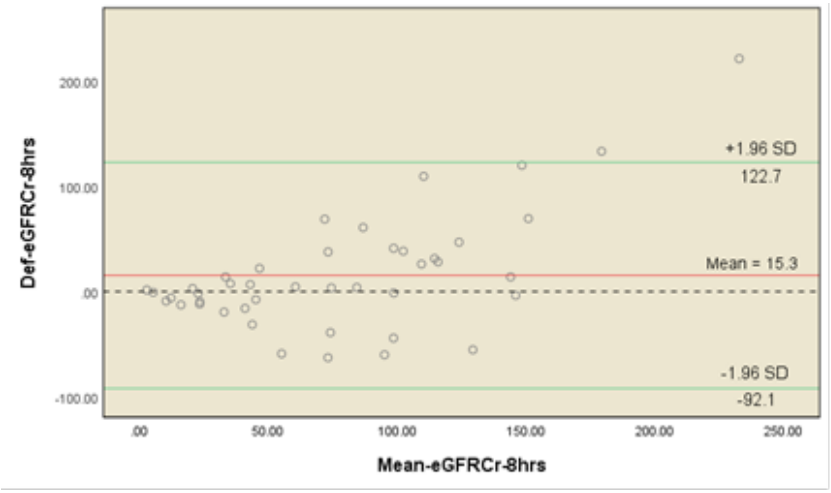
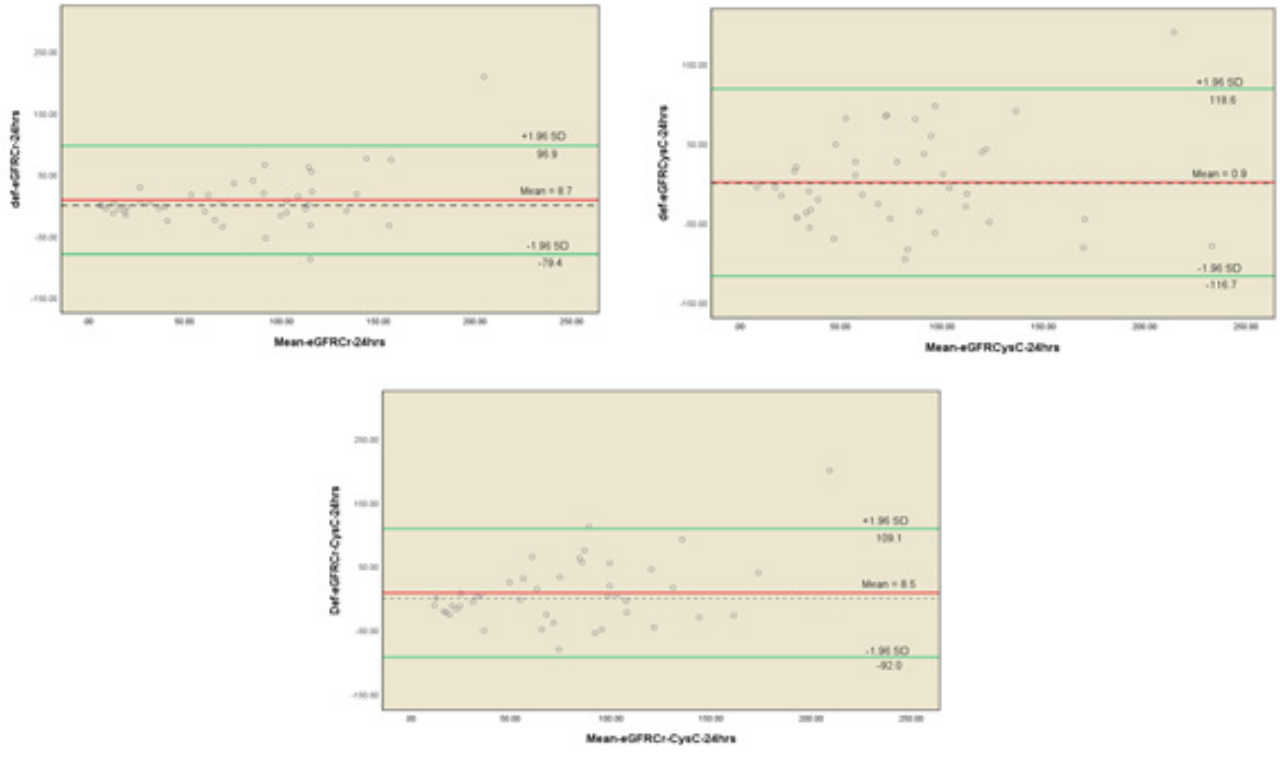
## *Accuracy, Bias, And Precision Analyses*

Bias, precision, and accuracy of each eGFR equations to CrCl are shown in Table III and Figure 2. At 24 hours, $eGFR_{Cr}$ had the highest accuracy with 30% and 50% accuracy of 53.5 and 74.4, respectively. The lowest accuracy was observed in $eGFR_{CysC}$ with accuracy within 30% and 50% of 18.6 and 46.5, respectively. At 72 hours, $eGFR_{Cr}$ had the highest accuracy within 30% and 50% of 60.04 and 51.32, respectively. $eGFR_{Cr}$ was also the most precise with the lowest SD mean bias of 45, However, $eGFR_{CysC}$ had the lowest bias with the mean difference of 0.9 at 24 hours, and 1.1 at 72 hours.

*(A): Bland Altman plots at 8 hrs*




*(B): Bland Altman plots at 24 hrs*



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*(C): Bland Altman plots at 72 hrs*

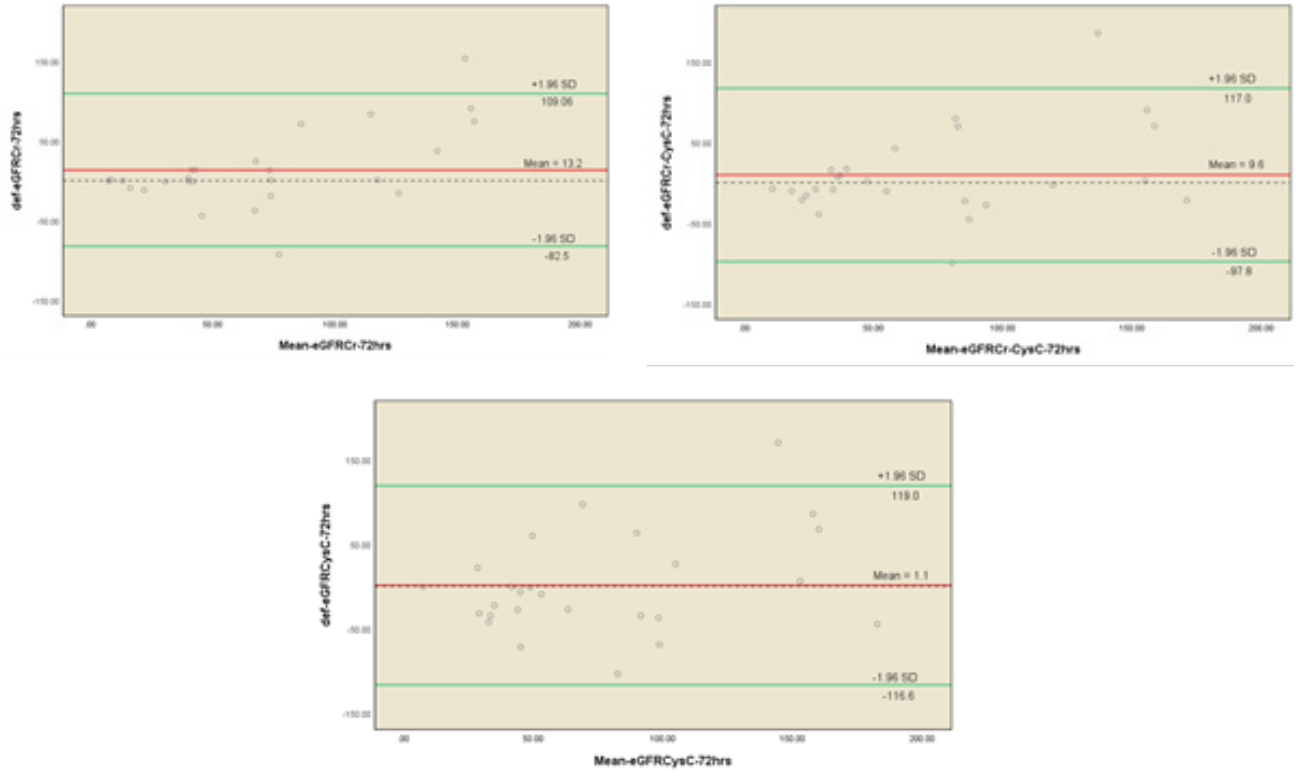


***Figure 2: Bland-Altman plots of the CrCL and eGFR$_{Cr}$, eGFR$_{CysC}$, and eGFR$_{Cr-CysC}$ (ml/min), showing the limits of agreement. The difference of CrCL was plotted against the mean of CrCL and eGFR. The mean difference was shown as a dotted horizontal line whereas the 95% limit of agreement was shown as the horizontal green lines. eGFR$_{CysC}$ showed the least bias among three equations. (A) eGFR$_{Cr}$ at 8 hrs (B) eGFR$_{Cr}$, eGFR$_{CysC}$, and eGFR$_{Cr-CysC}$ at 24 hrs (C) eGFR$_{Cr}$, eGFR$_{CysC}$, and eGFR$_{Cr-CysC}$ at 72 hrs.***

## *Subset Analysis of Patients with AKI and without AKI patients*

Of the 43 patients recruited, 12 (27.9%) had AKI based on KDIGO criteria. We evaluated the eGFR equations separately in patients with AKI and without AKI patients. Generally, eGFR equations correlated well with 24-hour CrCl in AKI patients only, but not in patients without AKI (Table II). Of all equations, eGFR$_{Cr}$ correlated best with 24-hour CrCl at all time points, with r of 0.799, 0.942 and 0.955 at 8, 24 and 72 hours respectively. In AKI patients, eGFR$_{Cr}$ were the least biased and most precise at 24 and 72 hours compared to eGFR$_{CysC}$ and eGFR$_{Cr-CysC}$ (Table III). In patients without AKI, eGFR$_{CysC}$ was the least bias, however eGFR$_{Cr}$ was still the most precise.

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*Table III: Bias, accuracy, and precision of estimated glomerular filtration rate (eGFR)*

| Time | Equation | Mean difference (bias) | SD of mean Bias<br>Precision | (Precision)<br>r2 | Accuracy within<br>30% | <br>50% |
|---|---|---|---|---|---|---|
| 8 hrs | $eGFR_{Cr}$ | 15.3 | 54.81 | 0.43 | 34.88 | 55.81 |
| 24 hrs | $eGFR_{Cr}$ | 8.7 | 45.00 | 0.48 | 53.49 | 74.42 |
| | $eGFR_{CysC}$ | 0.9 | 60.04 | 0.23 | 18.60 | 46.51 |
| | $eGFR_{Cr-CysC}$ | 8.5 | 51.32 | 0.33 | 37.21 | 53.49 |
| 72 hrs | $eGFR_{Cr}$ | 13.2 | 48.87 | 0.44 | 57.69 | 69.23 |
| | $eGFR_{CysC}$ | 1.1 | 60.11 | 0.22 | 30.77 | 46.15 |
| | $eGFR_{Cr-CysC}$ | 9.6 | 54.80 | 0.31 | 30.77 | 57.69 |

*eGFR, estimated glomerular filtration; CrCl, Creatinine clearance; Cr, creatinine; CysC, Cystatin C*

## The Diagnostic and Predictive Performance of eGFR Equations

$eGFR_{Cr}$ at 24 hours strongly diagnosed AKI at 24 hours and 72 hours (Table IV). $eGFR_{Cr}$ performed best in detecting AKI compared to the other two equations, with highest AUC of 0.938 and 0.844, respectively. $eGFR_{Cr-CysC}$ fare moderately with AUC 0.847 and 0.738 at 24 and 72 hours, respectively. All eGFRs were not predictive of mortality (Table IV).

*Table IV: Area Under Curve (AUC) of the Receiver Operating Characteristic (ROC) Curve for Diagnosis of Acute Kidney Injury and Prediction of Mortality*

| Time | Equation | AUROC (95% CI) | Lower bound | Upper bound | P value |
|---|---|---|---|---|---|
| Diagnosis of AKI | | | | | |
| 8hrs | CrCl | 0.777 | 0.586 | 0.967 | 0.005 |
| | $eGFR_{Cr}$ | 0.774 | 0.589 | 0.960 | 0.006 |
| 24hrs | CrCl | 0.879 | 0.733 | 1.000 | 0.000 |
| | $eGFR_{Cr}$ | 0.938 | 0.852 | 1.000 | 0.000 |
| | $eGFR_{CysC}$ | 0.688 | 0.518 | 0.859 | 0.058 |
| | $eGFR_{Cr-CysC}$ | 0.847 | 0.707 | 0.987 | 0.000 |
| 72hrs | CrCl | 0.706 | 0.478 | 0.935 | 0.082 |
| | $eGFR_{Cr}$ | 0.844 | 0.684 | 1.000 | 0.004 |
| | $eGFR_{CysC}$ | 0.700 | 0.499 | 0.901 | 0.092 |
| | $eGFR_{Cr-CysC}$ | 0.738 | 0.543 | 0.932 | 0.045 |
| Prediction of Mortality | | | | | |
| 8 h | CrCl | 0.536 | 0.311 | 0.761 | 0.779 |
| | $eGFR_{Cr}$ | 0.360 | 0.144 | 0.576 | 0.277 |
| 24 h | CrCl | 0.423 | 0.185 | 0.662 | 0.551 |
| | $eGFR_{Cr}$ | 0.446 | 0.208 | 0.684 | 0.674 |
| | $eGFR_{CysC}$ | 0.450 | 0.156 | 0.745 | 0.700 |
| | $eGFR_{Cr-CysC}$ | 0.464 | 0.184 | 0.743 | 0.779 |
| 72 h | CrCl | 0.432 | 0.109 | 0.754 | 0.670 |
| | $eGFR_{Cr}$ | 0.432 | 0.187 | 0.676 | 0.670 |
| | $eGFR_{CysC}$ | 0.602 | 0.288 | 0.916 | 0.522 |
| | $eGFR_{Cr-CysC}$ | 0.580 | 0.278 | 0.881 | 0.619 |

*CI, confidence Interval; AUROC, Area Under Receiver Operating Characteristic Curve; eGFR, estimated glomerular filtration; CrCl, Creatinine clearance; Cr, creatinine; CysC, Cystatin C*

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## DISCUSSION

The main aim of this study was to investigate which of the three CKD-EPI equations based on Cr ($eGFR_{Cr}$), CysC ($eGFR_{CysC}$) or combination of Cr and CysC ($eGFR_{Cr\text{-}CysC}$) best estimate measured GFR by 24-hour CrCl. Of the three equations, $eGFR_{Cr}$ had the highest correlation, accuracy, and precision with CrCl at 24 and 72 hours. The finding was similar in subset of patients with AKI (n=12). All equations contributed to the diagnosis of AKI, however none predicted in-hospital-mortality.

Previous studies that compared eGFR using CKD-EPI equations based on CysC and Cr with measured GFR showed conflicting results (4). $eGFR_{CysC}$ was shown to be more reliable for GFR assessment and clinical decision-making, as well as a better risk indicator for cardiovascular disease and mortality compared to $eGFR_{Cr}$ and $eGFR_{Cr\text{-}CysC}$ (21-24). Other studies showed that $eGFR_{Cr\text{-}CysC}$ has the greatest accuracy compared to $eGFR_{Cr}$ and $eGFR_{Cr\text{-}CysC}$. (25, 26,27). In a local study, $eGFR_{Cr}$ was shown to have the highest precision and accuracy to measured GFR by 51Cr-EDTA clearance compared to $eGFR_{Cr\text{-}CysC}$ and $eGFR_{CysC}$. (15). This finding was consistent with our study which showed that $eGFR_{Cr}$ equation had the highest correlation and highest accuracy with CrCl compared to $eGFR_{CysC}$, $eGFR_{Cr\text{-}CysC}$ at 24 and 72 hours. When patients were grouped in AKI and no AKI, this relationship was maintained in AKI patients only.

CysC is a potent inhibitor of cysteine proteases and is upregulated by corticosteroids suggesting that it could be upregulated in critically ill patients with the systemic inflammatory response syndrome (28). In our study most of our patients' primary diagnosis was infection (34.9%), indicating that CysC might be upregulated in these patients, and this partly explained the reason why CysC did not perform well. Another postulation of the poor performance of $eGFR_{CysC}$ is that CrCl that was considered as reference, was based on Cr hence resulting in a better result for $eGFR_{Cr}$ equation. In addition, CysC's volume of distribution varies in ICU patients with the volume status, hence further affecting its performance. We also postulate that $eGFR_{Cr}$ performed best in our ICU as most of our ICU patients had short stay, hence reduction in muscle mass did not influence $eGFR_{Cr}$.

We showed that CrCl and eGFR equations were strongly diagnostic of AKI. The AUC of $eGFR_{Cr}$ in predicting AKI was higher compared to CrCl, $eGFR_{CysC}$ and $eGFR_{Cr\text{-}CysC}$ at all time points. This finding is consistent with a study involving 203 emergency department patients, which showed that $eGFR_{Cr}$ was diagnostic of AKI with AUC of 0.70 (29). CrCl was also diagnostic of AKI, similar to a study on 484 ICU patients which showed that 4-hour CrCl helps in diagnosis of AKI with AUC of 0.87 (30). We postulate that the main reason that CysC based equations did not performed well is because AKI was diagnosed using creatinine definition, hence $eGFR_{Cr}$ performed best. In investigating the prognostic value of the eGFR, we observed that none of the equations predicted in hospital mortality in our study. This might be because of low sample size as it was not powered to the detection of mortality. This differs from the finding of a study on 3,298 participants that showed better performance of $eGFR_{CysC}$ compared to $eGFR_{Cr}$ in predicting 5-year and 10-year mortality (31).

### *Limitations of the study*

There were several limitations of the current study. First, the data originated from a single center with a small sample size. Second, the study lacked the gold standard of GFR measurement using tracer such as inulin or radioisotope clearance due to financial and technical limitations. Since the current available measurement for GFR which is available clinically in the ICU setting is 24-hour CrCl, we utilised it in this study. There is a limitation of overestimation of eGFR due to creatinine secretion with CrCl measurement. Third, anuric patients were excluded due to lack of urine for 24-hour CrCl measurement. Finally, the CKD-EPI equation was developed in CKD patients, but not in critically ill patients, hence further study developing or revising an equation in this population is warranted (32).

## CONCLUSION

$eGFR_{Cr}$ had the highest correlation to 24-hour CrCl and was the most accurate and precise equation. $eGFR_{CysC}$ equation had the lowest bias compared to eGFRCr and $eGFR_{Cr\text{-}CysC}$ at 24 and 72 hours. However, these comparisons are invalid in patients with anuric AKI due to lack of urine to allow for CrCl measurement. Hence future study utilising a tracer clearance as gold standard is important to evaluate the equations. Using ROC analysis, most of the equations contributed to diagnose AKI, however, none of the equation predicted in-hospital-mortality.

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## CONFLICT OF INTEREST

None

## ABBREVIATIONS

eGFR: Estimated glomerular filtration rate
CKD-EPI: Chronic Kidney Disease Epidemiology Collaboration
Cr: Creatinine
CysC: Cystatin C
CrCl: Creatinine clearance
$eGFR_{Cr}$: Estimate glomerular filtration rate from serum creatinine
$eGFR_{CysC}$: Estimate glomerular filtration rate from serum Cystatin C
KDOQI: National Kidney Foundation Disease Outcomes Quality Initiative
APACHE II: Acute Physiology and Chronic Health Evaluation II
SOFA: Sequential Organ Failure Assessment
KDIGO: Kidney Disease Improving Global Outcome
MDRD: Modified Diet in Renal Disease
ICU: Intensive Care Unit

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Editorial

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# CHALLENGES OF MANAGING A CASE OF WORSENING ACUTE KIDNEY INJURY IN ACTIVE LUPUS NEPHRITIS WITH SUPERIMPOSED COVID-19 INFECTION: A CASE REPORT

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## ABSTRACT

We present a challenging case of a young man with known lupus nephritis who came to us with a flare of lupus nephritis and superimposed COVID-19 infection. The use of immunosuppressant in lupus nephritis flare with concurrent infection remains a concern of igniting overwhelming infection. Despite high dose prednisolone and dialysis, we noticed worsening in his renal function. He subsequently received intravenous immunoglobulin (IVIG) as rescue therapy that resulted in clinically and biochemically improvement. He was discharged to home well with improved renal function. However, future clinical trials are required to conclude our observation if IVIG rescue therapy in an acute flare of lupus nephritis with concurrent COVID-19 pneumonia remains to be a feasible treatment option. Furthermore, the association and causation of acute flare of lupus nephritis caused by COVID-19 infection remain to be explored.

***Keywords:*** *Lupus nephritis, intravenous immunoglobulin, Covid-19*

## INTRODUCTION

Systemic lupus erythematosus (SLE) is an autoimmune disease in which the immune system attacks its tissues, causing widespread inflammation and tissue damage in the affected organs. It can affect the joints, skin, brain, lungs, kidneys, and blood vessels. The prevalence of SLE patients developing Lupus Nephritis (LN) varies between different regions of the world, races, and ethnicities. In the United States, we can see a higher prevalence of LN among black populations. Asian SLE patients have a higher prevalence of LN compared to Caucasian SLE patients. Asians often present with more severe diseases. Up to 10% of LN patients will develop end-stage renal disease (ESRD). The risk of ESRD is higher in a certain subgroup of LN such as Class IV (diffuse LN) which is as high as 44% over 15 years. More importantly, by achieving complete disease remission, the patient 10-year survival rate is 95% as compared to 43% for those with no remission.

The reports for the incidence of COVID-19 patients with an autoimmune disorder were scarce. Despite few case reports having been published on the possible association between autoimmune disorders and COVID-19, the role of this virus in these conditions remains unclear.

## CASE PRESENTATION

We report a case of a 28-year-old male with an acute flare of lupus nephritis with concurrent COVID-19 infection. He has a medical history of SLE, and Lupus Nephritis complicated with chronic kidney disease (class IV LN based on renal biopsy on August 2020). He had multiple histories of the flare of lupus nephritis previously, precipitated by non-compliance to medication. His recent flare episode was a week before his admission

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for COVID-19 infection. During the admission for the acute flare on lupus nephritis, he was pulsed with IV Methylprednisolone 500mg daily for 3 days and given a STAT dose of IV Cyclophosphamide 500mg as a part of the EUROLUPUS regime. He was discharged with a tapering dose of prednisolone, hydroxychloroquine and he complied with the treatment this time. At the time of discharge, he was well clinically, and his renal profile improved.

A week after being discharged, he presented with acute onset of fever (38ºC), non-productive cough, progressive dyspnea, and worsening abdominal swelling. He denied any contact with COVID-19 patients and no exposure to high–risk patients during his recent admission.

On physical examination, he was in mild respiratory distress with a respiratory rate of 22 but was able to speak in full sentences. Lung's auscultation revealed reduced breath sound bilateral lower zone and abdominal ascites. Mild pedal edema was also noted to the level of mid-shin. Oxygen saturation was 97% on room air and other vital signs were stable. At his presentation to the emergency department, he did not require any oxygenation support despite mild respiratory distress as saturation was able to maintain > 95% on room air. His initial diagnosis was COVID-19 pneumonia category 3 with lupus nephritis flare.

The first test performed was a COVID-19 Antigen Rapid Test Kit which was positive. His COVID-19 Real-Time – Polymerase Chain Reaction swab had shown a cycle threshold (CT) value of 28. His blood and urine laboratory parameters concurred with the flare of lupus nephritis and acute renal failure (Fig. 1) and his chest X-ray on admission showed bilateral peripheral opacities which is one of the features of COVID-19 Pneumonia. Other laboratory findings showed urea 50.7mmol/L, creatinine 865 µmol/L, eGFR 7 mL/min/1.73m2, CRP 33.65mg/L (normal range < 5mg/L) and WCC 11.2 x109 (normal range 4-11 x109). His baseline renal profile was urea 37mmol/L, creatinine 195umol/L, eGFR 41 one week before admission.

The initial treatment given in the emergency setting was intravenous frusemide 40mg STAT dose with subcutaneous low molecular weight heparin (LMWH) 40mg as DVT prophylaxis. In terms of steroids, he was continued on prednisolone 50mg once daily started on this admission for the acute flare of nephritis. He had urgent hemodialysis via the femoral catheter after consulting a nephrologist.

Throughout his stay inward, we noticed worsening renal function despite adequate urine output and regular dialysis. In terms of COVID-19 pneumonia, there was no disease progression or respiratory distress requiring oxygen support, and it remained at category 3. A decision was made for intravenous immunoglobulin (IVIG) as the lupus flare was not improving despite being given a high dose of prednisolone. IVIG was given a total of 90g in 2 divided doses on day 6 of admission. There was a delay in the initiation of IVIG due to the patient's financial constraints. Renal profile following IVIG had shown improvement with urea 31mmol/L and creatinine 303umol/L. Repeated urine protein: creatinine ratio was 655mg/mmoL (normal range <50mg/mmoL) and urine for examination and microscopy showed protein 3+. The patient improved clinically and biochemically after a few days of IVIG administration. The patient was counseled for a repeat renal biopsy but refused. He was then discharged with a tapering dose of prednisolone and regular frusemide as clinically all the presented symptoms resolved, and his vitals were stable. A nephrology clinic appointment was given 4 weeks after discharged and he was given cyclophosphamide as the continuation of the subsequent EUROLUPUS regime. Renal profile during clinic appointment further improved with urea 20.3mmol/L and creatinine 250umol/L. We summarized the serial laboratory workup in the table below (Table 1.)

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| LABORATORY INVESTIGATIONS | Equation Baseline (4 months prior admission) | Baseline (1-week prior admission after given methylprednisolone and cyclophosphamide) | On admission (Before treatment with IVIG) | Upon discharge (After treated with IVIG) | During renal clinic appointment (After discharge) |
|---|---|---|---|---|---|
| Hb (13-17g/L) | 14.7 | 14.9 | 13.0 | | |
| WCC (4-10 x10^9) | 3.7 | 5.2 | 11.2 | | |
| PLT (150-400 ¯x10^9) | 158 | 172 | 206 | | |
| CRP (<5.00mg/L) | | 4.85 | 33.65 | 3.44 | 6.35 |
| ESR (<21mm/hr) | | 23 | 45 | | 11 |
| Urea (3.2-8.2mmol/L) | 6.5 | 37 | 50.7 | 31 | 20.3 |
| Creatinine (54-97umol/L) | 87 | 195 | 865 | 303 | 250 |
| Urine PCR<br>UFEME | 341.6<br>3+ | 689<br>3+ | 1029<br>3+ | 655<br>3+ | 545.1<br>3+ |
| Anti-dsDNA (0-200iU/mL) | | | 148 | | 52 |
| C3 (90-180mg/dL) | | | 80 | | 112 |
| C4 (10-40mg/dL) | | | 44 | | 49 |

*Table 1. Laboratory investigations at baseline, during admission, upon discharge, and during renal clinic appointments.*

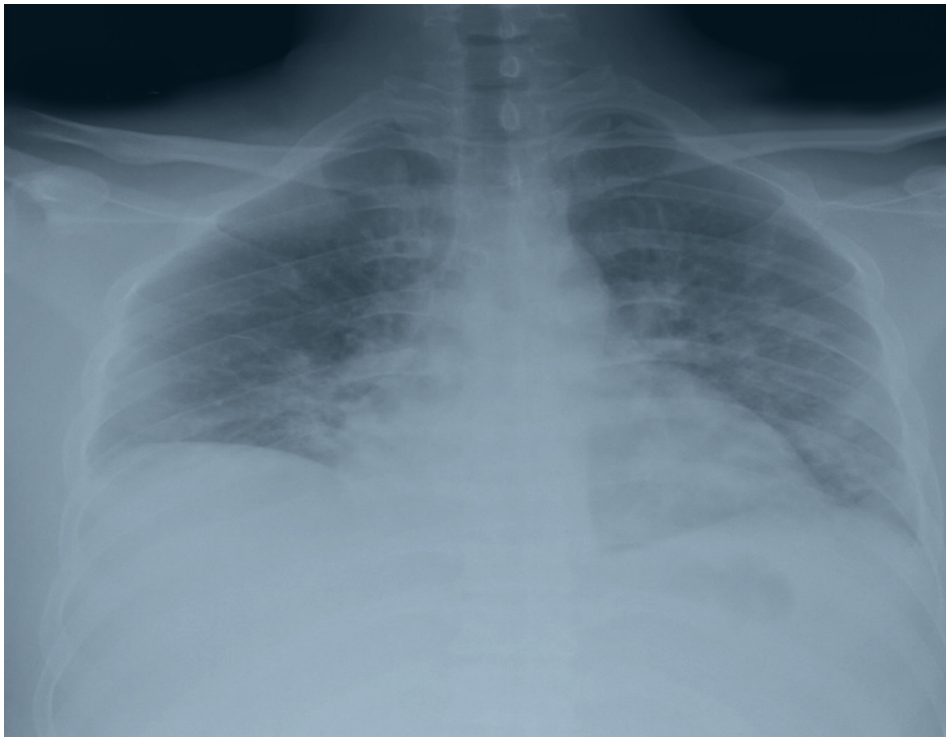

*Fig. 1. Chest X-Ray depicting bilateral interstitial infiltrates which are the features of both lupus nephritis and COVID-19 Pneumonia*

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## DISCUSSION

In this case report, a puzzling scenario was encountered. Our patient had COVID-19 Pneumonia with a concurrent acute flare of lupus nephritis. His presenting symptoms of fever, cough, shortness of breath, abdominal distension, and bilateral lower limb swelling can be observed both in lupus and COVID-19 Pneumonia. Lymphopenia on the other hand can be a hallmark feature in both disorders. Previous studies reported that certain viruses may be related to the pathophysiology of SLE flare. Epstein-Bar virus (EBV), cytomegalovirus, and parvovirus B19 are some of the many possible triggers for SLE. There is also a reported case of dengue fever evolving into a lupus flare. They found that the dengue virus has triggered a dysfunctional immune response that resulted in the development of SLE, lupus nephritis [1]. Otherwise, the exact pathophysiology behind it remains unclear.

There are limited data on the association and causation of COVID-19 pneumonia triggering lupus nephritis flare; and the treatment option for lupus nephritis flare during COVID-19 pneumonia. One case reported from Kashan Rheumatology Clinic showed that the patient developed a flare of lupus nephritis after 2 months post COVID-19 infection. The patient was treated with methylprednisolone for 3 days, maintenance of prednisolone and hydroxychloroquine, and his symptoms improved [3]. Another case was reported in Riyadh, Saudi Arabia, where COVID-19 infection triggered a lupus flare, lupus pneumonitis. The patient was treated with methylprednisolone and tapering oral steroids and was discharged well [4]. Our approach was different from the above-reported cases whereby we used IVIG as rescue therapy in the case of acute flare during the acute phase of COVID-19 infection.

Our patient was initially treated with high-dose prednisolone to cover both COVID-19 and flare of lupus nephritis. However, due to the worsening renal function despite on high dose prednisolone and dialysis, he was decided for intravenous Immunoglobulin (IVIG). This IVIG rescue therapy was deemed to be the best option to treat acute flare of resistant lupus nephritis moreover with the presence of ongoing infection, in this case, COVID-19 pneumonia. IVIG has been proven to be effective in treatment-resistant membranous or membranoproliferative lupus nephritis [2]. Besides, observations have been reported that IVIG can potentially be an effective adjunct treatment for COVID-19 pneumonia. A pilot study in San Diego, California reported that IVIG 0.5 g/kg daily for 3 days with concomitant methylprednisolone 40 mg reduced progression of respiratory failure requiring mechanical ventilation, the total length of hospital stay, and ICU length of stay, and improved oxygenation at 7 days in COVID-19 patients [5]. Shao et al identified that early IVIG administration significantly reduces the 28-day mortality rate, improves some organ functions, and decreases inflammatory response in severe COVID-19 patients [6]. This can be explained by the fact that viremia develops within the first week of infection. Subsequently, the primary immune response emerges in the blood circulation by day 10–14 and is followed by viral clearance. Additionally, FJF Herth et al demonstrated that IVIG appeared to improve the clinical symptoms, chest imaging, and laboratory investigations. Patients who received IVIG earlier showed a shorter duration of hospital stay [7]. These reports possibly explain why our patient did not progress to the worsening category of COVID-19 pneumonia.

Nevertheless, P Tabarsi et al did not support the use of IVIG in combination with hydroxychloroquine and lopinavir/ritonavir in the treatment of severe COVID-19 cases [8]. The usage of IVIG in the case of acute lupus flare with concurrent COVID-19 infection remains uncertain especially in the Asian population who has more aggressive lupus nephritis. To date, COVID-19 Treatment Guidelines Panel recommends against the use of IVIG for the treatment of acute COVID-19, except in clinical trials.

## CONCLUSION

Our case report illustrated that IVIG rescue therapy for an acute flare of lupus nephritis in the presence of ongoing COVID-19 pneumonia can be potentially a feasible and safe treatment. However, future clinical trials are required to conclude our observation as the current treatment for COVID-19 pneumonia perse do not recommend the use of IVIG. Furthermore, the association and causation of acute flare of lupus nephritis caused by COVID-19 infection remain to be explored.

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